



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07H 21/00, C12N 1/15, 1/21, 5/10, 15/11, 15/63</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/31117</b> <b>(43) International Publication Date:</b> 24 June 1999 (24.06.99)																																							
<b>(21) International Application Number:</b> PCT/US98/27059 <b>(22) International Filing Date:</b> 17 December 1998 (17.12.98)  <b>(30) Priority Data:</b> <table border="0"> <tr><td>60/070,923</td><td>18 December 1997 (18.12.97)</td><td>US</td></tr> <tr><td>60/068,007</td><td>18 December 1997 (18.12.97)</td><td>US</td></tr> <tr><td>60/068,057</td><td>18 December 1997 (18.12.97)</td><td>US</td></tr> <tr><td>60/068,006</td><td>18 December 1997 (18.12.97)</td><td>US</td></tr> <tr><td>60/068,008</td><td>18 December 1997 (18.12.97)</td><td>US</td></tr> <tr><td>60/068,054</td><td>18 December 1997 (18.12.97)</td><td>US</td></tr> <tr><td>60/068,064</td><td>18 December 1997 (18.12.97)</td><td>US</td></tr> <tr><td>60/068,053</td><td>18 December 1997 (18.12.97)</td><td>US</td></tr> <tr><td>60/068,169</td><td>19 December 1997 (19.12.97)</td><td>US</td></tr> <tr><td>60/068,368</td><td>19 December 1997 (19.12.97)</td><td>US</td></tr> <tr><td>60/068,367</td><td>19 December 1997 (19.12.97)</td><td>US</td></tr> <tr><td>60/068,369</td><td>19 December 1997 (19.12.97)</td><td>US</td></tr> <tr><td>60/068,365</td><td>19 December 1997 (19.12.97)</td><td>US</td></tr> </table> <b>(71) Applicant (for all designated States except US):</b> HUMAN GENOME SCIENCES, INC. [US/US]; 9410 Key West Avenue, Rockville, MD 20850 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> MOORE, Paul, A. [US/US]; 19005 Leatherbark Drive, Germantown, MD		60/070,923	18 December 1997 (18.12.97)	US	60/068,007	18 December 1997 (18.12.97)	US	60/068,057	18 December 1997 (18.12.97)	US	60/068,006	18 December 1997 (18.12.97)	US	60/068,008	18 December 1997 (18.12.97)	US	60/068,054	18 December 1997 (18.12.97)	US	60/068,064	18 December 1997 (18.12.97)	US	60/068,053	18 December 1997 (18.12.97)	US	60/068,169	19 December 1997 (19.12.97)	US	60/068,368	19 December 1997 (19.12.97)	US	60/068,367	19 December 1997 (19.12.97)	US	60/068,369	19 December 1997 (19.12.97)	US	60/068,365	19 December 1997 (19.12.97)	US	20874 (US). RUBEN, Steven, M. [US/US]; 18528 Heritage Hills Drive, Olney, MD 20832 (US). CARTER, Kenneth, C. [US/US]; 11601 Brandy Hall Lane, North Potomac, MD 20878 (US). SHI, Yang-gu [CN/US]; 437 West Side Drive, Gaithersburg, MD 20878 (US). ROSEN, Craig, A. [US/US]; 22400 Rolling Hill Road, Laytonsville, MD 20882 (US). SOPPET, Daniel, R. [US/US]; 15050 Stillfield Place, Centreville, VA 22020 (US). KYAW, Hla [MM/US]; 520 Sugarbush Circle, Frederick, MD 21703 (US). WEI, Ying-Fei [CN/US]; 1714-C Marina Court, San Mateo, CA 94403 (US). FLORENCE, Kimberly [US/US]; 12805 Atlantic Avenue, Rockville, MD 20851 (US). DUAN, Roxanne, D. [US/US]; 5515 Northfield Road, Bethesda, MD 20817 (US). FLORENCE, Charles [US/US]; 12805 Altantic Avenue, Rockville, MD 20851 (US). GREENE, John, M. [US/US]; 872 Diamond Drive, Gaithersburg, MD 20878 (US). FENG, Ping [CN/US]; 4 Relda Court, Gaithersburg, MD 20878 (US). FERRIE, Ann, M. [US/US]; 120 Fox Run Drive, Tewksbury, MA 01876 (US). YU, Guo-Liang [CN/US]; 1714-C Marina Court, San Mateo, CA 94403 (US). JANAT, Fouad [SY/US]; 140 High Street, No. 202, Westerly, RI 02891 (US). NI, Jian [CN/US]; 5502 Manorfield Road, Rockville, MD 20853 (US).  <b>(74) Agents:</b> BROOKES, A., Anders et al.; Human Genome Sciences, Inc., 9410 Key West Avenue, Rockville, MD 20850 (US).  <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
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<b>(54) Title:</b> 110 HUMAN SECRETED PROTEINS  <b>(57) Abstract</b> <p>The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.</p>																																									

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## 110 Human Secreted Proteins

### *Field of the Invention*

This invention relates to newly identified polynucleotides and the polypeptides encoded by these polynucleotides, uses of such polynucleotides and polypeptides, and  
5 their production.

### *Background of the Invention*

Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or  
10 organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic reticulum  
15 (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

Proteins targeted to the ER by a signal sequence can be released into the  
20 extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in secretory vesicles (or  
25 secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

Despite the great progress made in recent years, only a small number of genes encoding human secreted proteins have been identified. These secreted proteins include  
30 the commercially valuable human insulin, interferon, Factor VIII, human growth hormone, tissue plasminogen activator, and erythropoietin. Thus, in light of the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical disorders by using  
35 secreted proteins or the genes that encode them.

### *Summary of the Invention*

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, and recombinant methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting disorders related to the polypeptides, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying binding partners of the polypeptides.

### *Detailed Description*

#### **Definitions**

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig



analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard,  
5 Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained  
10 in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42°C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the  
15 filters in 0.1x SSC at about 65°C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages  
20 of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH<sub>2</sub>PO<sub>4</sub>; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even  
25 lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include  
30 Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such  
35 as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a

complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

5           The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be  
10           single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability  
15           or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

          The polypeptide of the present invention can be composed of amino acids joined  
20           to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs,  
25           as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be  
30           branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a  
35           nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine,

formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS -  
5 STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990);  
10 Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

"SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting  
15 activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present  
20 invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)

## 25 Polynucleotides and Polypeptides of the Invention

### FEATURES OF PROTEIN ENCODED BY GENE NO: 1

30 The translation product of this gene shares sequence homology with a neurogenic secreted signaling protein, in addition to the human UDP-galactose:2-acetamido-2-deoxy-D-glucose3beta-galactosyltransferase (See Genbank Accession No. gnllPIDle1237254 ) which is thought to be vital in glycoprotein biosynthesis. In specific embodiments, polypeptides of the invention comprise the following amino acid  
35 sequence: GLGPAQVALSLQGPA (SEQ ID NO:239), SSWMAGTQPRTSWWEMSS AKPCPTGTLRSNTSSHPQCTGPPTTHPMLVGEDMSCPEPQCGASRLSWKMNS

SPLMMSLWVCA (SEQ ID NO:240), QPRTSWWEMSSAKPCPTGTLRSN (SEQ ID NO:241), MSCPEPQCGASRLSWKMLNSSPL (SEQ ID NO:242), WVALLYEG GMKYLT LVLLGRAWRM TSPTRRSWAGSQPSRNSNTLGTWTKTSSSPFSMK WAWGQAATTQRCRCSSLSVRLKKSSVKSHWRMSSNSLLS (SEQ ID NO:243),  
 5 GGMKYLT LVLLGRAWRM TSPTRRSWAGSQPSRNSNTLGTWTKTSSSPFSMKW (SEQ ID NO:245), and/or TTQRCRCSSLSVRLKKSSVKSHWRMS (SEQ ID NO:246). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a  
 10 marker in linkage analysis for chromosome 12.

This gene is expressed primarily in human fetal brain, epileptic frontal cortex and 12 week old early stage human.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
 15 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural or immune disorders, particularly neurodegenerative conditions such as epilepsy. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,  
 20 particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene  
 25 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:125 as residues: Ala-27 to Ser-38, Pro-43 to Asn-54, Thr-115 to Asp-121, Leu-225 to Val-232, Pro-247 to Gly-252, Arg-306 to Leu-311.

30 The tissue distribution in fetal brain tissue, combined with the homology to a neurogenic secreted signaling protein, in addition to the conserved UDP-galactose:2-acetamido-2-deoxy-D-glucose 3beta-galactosyltransferase protein indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment, detection, and/or prevention of a variety of neural disorders, particularly  
 35 epilepsy and other disorders of the CNS. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are

not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, 5 paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, 10 neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. In addition, the protein may show utility in the creation of novel therapeutics which depend upon the localizing benefits (cell and tissue specificity) of glycoproteins. This protein may also be used to produce physiologically active saccharide chains and variants, and for improvement of saccharide chains bound to physiologically active 15 proteins. Expression within fetal tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be 20 involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ 25 ID NO:11 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of 30 a-b, where a is any integer between 1 to 1257 of SEQ ID NO:11, b is an integer of 15 to 1271, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.

## 35 FEATURES OF PROTEIN ENCODED BY GENE NO: 2

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ASTLAQ

TTGTCKXXXSSRRARSRTQRXFQLRPDKRSAPSLQFIQAQEELSKENTGRQLA  
 AREAVLALEGSTQLTG PVTQVAASKTHCSGMALTASPVPVLGAAPAKXPTQ  
 5 NXPGQXGRAXXKVXTSWXXVATKVLHGLEVSTHLGKRKLSGRSWLPGP  
 ALHATPSQSHTQTGSQIVHPPQGEVREVGRGRGQPPAQPVHAHPSQQHPSPAH  
 LAGLSLWTGTA (SEQ ID NO:247), AMLETWRPGPSXGELATNSGQRASQDSQ  
 HSPPHVRAHLLISPLPAFPSMGGPAGRSAPXXLTETKSELQRLRRRQARASXS  
 XPAGEPGAGHSDSFNCVPTNGQPLRSCSLSKLRRSFLKRTQGDSWLPEKQSW  
 10 LWKAPPS (SEQ ID NO:248), SHQSHLINPASSAKGSAQLKAQPPAHVLGGT  
 GQEGPPPTADQPESPGWDPSSFTNGSSGPRALPTS VHPTLQQGAPCRRNWA  
 PCRGLVETRMRLRRQLPHGTSKRDLGWASLQRGSPQETPQ (SEQ ID NO:249),  
 RPDKRSAPSLQFIQAQEELSKENTGRQLAAREAV (SEQ ID NO:250), ATPSQ  
 SHTQTGSQIVHPPQGEVREVGRGRGQPP (SEQ ID NO:251), QDSQHSPPHVR  
 15 AHLLISPLPAFPSMGGPA (SEQ ID NO:252), DSFNCVPTNGQPLRSCSL  
 KLRRSFLKR (SEQ ID NO:253), KGSWAQLKAQPPAHVLGGTGQEGPP (SEQ ID  
 NO 254:), KPSHQP (SEQ ID NO:256), and/or APSLLQFIQAQEELSKENTGRQLA  
 AR (SEQ ID NO:255). Polynucleotides encoding these polypeptides are also  
 encompassed by the invention.

20 This gene is expressed exclusively in adult human testis.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions which include, but are  
 not limited to, reproductive disorders, particularly abnormalities of the testis, in addition  
 25 to impotence and infertility. Similarly, polypeptides and antibodies directed to these  
 polypeptides are useful in providing immunological probes for differential identification  
 of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,  
 particularly of the male reproductive system, expression of this gene at significantly  
 higher or lower levels may be routinely detected in certain tissues or cell types (e.g.,  
 30 reproductive, testicular, adrogen regulated, and cancerous and wounded tissues) or  
 bodily fluids (e.g., lymph, serum, plasma, seminal fluid, urine, synovial fluid and  
 spinal fluid) or another tissue or cell sample taken from an individual having such a  
 disorder, relative to the standard gene expression level, i.e., the expression level in  
 healthy tissue or bodily fluid from an individual not having the disorder.

35 Preferred epitopes include those comprising a sequence shown in SEQ ID  
 NO:126 as residues: His-45 to Gly-56, Trp-62 to Tyr-68, His-94 to Trp-100.

The tissue distribution in testis indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention for abnormalities of the reproductive system. In addition, expression of this gene product in the testis may implicate this gene product in normal testicular function. This gene product may be useful in the treatment of male infertility, and/or could be used as a male contraceptive. Moreover, the protein product of this gene may be useful in the treatment, detection, and/or prevention of a variety of disorders related to androgen-regulated tissues, particularly the prostate gland. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:12 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1437 of SEQ ID NO:12, b is an integer of 15 to 1451, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 3

The translation product of this gene shares sequence homology with the human VAKTI precursor (See Genbank Accession No. gnllPIDle1311078 (AJ228139)), in addition to the ovoinhibitor and thrombin inhibitors, which are thought to be important in inhibition of protease activities. Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of monocytes to calcium. Thus, it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of both immune cells, in addition to other cell-lines or tissue cell types. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating monocytes. Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium and sodium, as well as alter pH and membrane potential. Alterations in small molecule concentration can be measured to identify supernatants which bind to

receptors of a particular cell. Moreover, when tested against NIH3T3 and U937 cell lines, supernatants removed from cells containing this gene activated the EGR1 (early growth response) and GAS (gamma activating sequence) promoter elements. Thus, it is likely that this gene activates fibroblasts or hematopoietic cells through the EGR1 and/or

5 JAK-STAT signal transduction pathway. EGR1 is a separate signal transduction pathway from Jak-STAT, genes containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. GAS is also a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal

10 transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: CSYRPQFPVDPRVRATCIVFN (SEQ ID NO:257), GTENLLA

15 PERTILSRAQMGKCMATPAPCVRSSSKQKKKKRKRKRVXQETKDNLRVQLPL XSCVVNXANPGKTDGFFAPERMTSPRAQMEKCMATPAPCVRPSFNKKKEQE QRLKEKLQRKSAVNFGTK (SEQ ID NO:258), LLAPERTILSRAQMGKCMAT PAPCVR (SEQ ID NO:259), PGKTDGFFAPERMTSPRAQMEKCM (SEQ ID NO:260), EQRLKEKLQRKSAVNFG (SEQ ID NO:261), KTLLENFSTQGTFFVAMH

20 PAVRATDWITLPCTKKPSISHLFFXFLAKILFSISSNSSFTLSLGIFSFFXXQLST HCTLIAMRLPIRTKNRIIFPCASKSSISNKGPKSTAYILLWITALTFPFTFYTNL GPGFRILSTQCTSVVICFPICATNSFIIIRTDKIPISFSFFKIITIQLC WGSSLGSSC (SEQ ID NO:262), MHPAVRATDWITLPCTKKPSIS (SEQ ID NO:263), LIAMRLP IRTKNRIIFP (SEQ ID NO:264), SSISNKGPKSTAYILL WITALTFPFT (SEQ ID NO:265), IIIRTDKIPISFSFFKIITIQLC (SEQ ID NO:266), NDGQCLAYNTTHY

25 RERAMTSHARVSLGPSRDPLERPPFFFFFFFFFFFFKFEHTGTHGTLVSMHFAI WATDRIMLPGAYKCSIPHLVPKFTADFLCSFSFSLCSCSFLLKEGLTHGAGVA MHFSIWALDGVILSGAKKPSVFPGFAXFTTQLXKGCTL RLSFVS (SEQ ID NO:267), CLAYNTTHYRERAMTSHARVSL (SEQ ID NO:268), GTLVSMHFAI

30 WATDRIMLPGAYKCSIPHLVP (SEQ ID NO:269), GVILSGAKK PSVFPGFAX FTTQLX (SEQ ID NO:270), KKASHMEQVLP CIPSGPWMGSFSLXQKSRPF FLDLRXSLHNSXKEAVLLDCLLFLXXPSFFFFSSSSAWKKTSHMEQVLPCT FPSGPWIGLFSLVQASFPFLTSFRYSLQSSAYEVAFPDSSLFLARASAFFSSFSFA WK (SEQ ID NO:271), CIPSGPWMGSFSLXQKSRPF FLDLRXS (SEQ ID

35 NO:272), WIGLFSLVQASFPFLTSFRYSLQSSAYE (SEQ ID NO:273), NSAVN IKIRQRMEYFSVPEKMTL FVVQMGKCMATCVPCVKPTSQKQMKKRKRLKHE LETKENLEKQPHMQSFVNIESL (SEQ ID NO:274), IKIRQRMEYFSVPEKMTL



FVVQM (SEQ ID NO:275), and/or VKPTSKQKMKKRKRLKHELETKENL (SEQ ID NO:276). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in

5 linkage analysis for chromosome 5.

This gene is expressed primarily in heart, tonsils, Hodgkin's lymphoma, neuroblastoma, leukocyte and lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
10 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cardiovascular, immune, or hemodynamic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the circulatory system,  
15 expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cardiovascular, muscle, immune, hematopoietic, pulmonary, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, pulmonary surfactant or sputum, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative  
20 to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:127 as residues: Ala-20 to Gln-27.

The tissue distribution in heart and immune cells and tissues, the homology to  
25 protease inhibitors, in addition to the detected calcium flux, EGR1, and GAS biological activities indicates polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of hemodynamic or vascular disorders, including hemorrhage, heart failure, and embolism, because proteases and their inhibitors are often involved in the cascades controlling hemodynamic controls. Protein may also  
30 show utility in the treatment, detection, and/or prevention of a variety of metabolic (i.e. cellular or physiological) and/or proliferative disorders in which aberrant regulation of a protease is thought to be involved, particularly in the premature activation of zymogens, for example. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify  
35 agents that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological activities. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines;

immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2303 of SEQ ID NO:13, b is an integer of 15 to 2317, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 4

The translation product of this gene shares sequence homology with the ecotropic retrovirus receptor and the human cationic amino acid transporter-3 (See Genbank Accession No. gnllPIDle1198517) which are thought to be important in viral infections and amino acid and polyamine transport. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

PRVRGTVVRLRQHRPSAYILVSTVLTLMVPWHS�DPDSALADAFYQRGYRWAG  
 FIVAAGSICA (SEQ ID NO:277), TVVRLRQHRPSAYILVSTVLTLMVP (SEQ ID  
 NO:278), WHSLDPDSALADAFYQRGYRWAGFIV (SEQ ID NO:279), TPSCSASS  
 SPCHALSMPWPPMGSSSRCLPMCTPGHRCLWRAPWRSGSSRPSWHCCWTWS

RWFSSCPLAHSWPTHSWPPVSLCCASRSLPRPAPQAQPALAP (SEQ ID NO:280), LSMPWPPMGSSSRCLPMCTPGHRC (SEQ ID NO:281), APWRSGSS RPSWHCCWTWSRWFSSCPL (SEQ ID NO:282), THSWPPVSLCCASRSL PRPAPQ (SEQ ID NO:283), AYILVSTVLTLMPVHSLDPDSALADAFYQRGYRW  
 5 AGFIVAAGSICAMNTVLLSLLFSLP (SEQ ID NO:284), PWHSLDPDSALADAF YQRGYRWAGFIVAAGS (SEQ ID NO:285), RIVYAMAADGLFFQVFAHVHPRTQ VPV (SEQ ID NO:286), DLESLVQFLSLGTLLA (SEQ ID NO:287), YTFVATSII VLRFAQK (SEQ ID NO:288), LTKQQSSFSDDLQVGTVHASVPEPGELKPA (SEQ ID NO:289), LRPYLGFLDGYSPPGAVVTWALGVMLASAITIGCVLVFGNSTL  
 10 HLPHWGYI (SEQ ID NO:290), PGAVVTWALGVMLASAITIGCVLVFGN (SEQ ID NO:291), GAHQQQYREDLFQIPMVPLIPALSIVLNICLMLKLSYLTWVRFSTW LLMGLAV (SEQ ID NO:292), MVPLIPALSIVLNICLMLKLSYLTWV (SEQ ID NO:293), and/or YFGYGIRHSEKENQRELPLNSTHYVVFPR (SEQ ID NO:294).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

15 This gene is expressed primarily in placenta and brain tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, neural, or metabolic disorders, in addition to viral  
 20 infections. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and placenta, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g.,  
 25 reproductive, neural, hepatic, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, bile, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:128 as residues: Gln-87 to Ser-99, Pro-102 to Phe-110, Gln-204 to Leu-211, Ser-262 to Glu-268, Pro-294 to His-305.

The tissue distribution in placenta, combined with the homology to a retroviral receptor and cationic amino acid transporters, indicates polynucleotides and  
 35 polypeptides corresponding to this gene are useful for the diagnosis and intervention of viral infections, or diseases and malfunctions related to amino acid transport. Specifically, soluble forms of this protein or, polynucleotides of the present invention,

can be used to bind to retroviruses so as to prevent their entry and infection of susceptible cells. They can be used for therapy/prevention of HIV infection and certain forms of leukaemia. Polynucleotide or polypeptides of the present invention can be used to identify susceptibility to retroviral infection. Based upon the tissue distribution

5 in the brain, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma,

10 congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain

15 indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:14 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

25 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1458 of SEQ ID NO:14, b is an integer of 15 to 1472, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where b is greater than or equal to a + 14.

30

### FEATURES OF PROTEIN ENCODED BY GENE NO: 5

In specific embodiments, polypeptides of the invention comprise the following

35 amino acid sequence: FPPSPAPPHSLPLRSWLWSRQMG (SEQ ID NO:295), GTSF RGMISTQPGSTPLASFKILALESADGHGGCSAGNDIGPYGERDDQVFIQKVVP SASQLFVRLSSTGQRVCSVRSVDGSPTTAFTVLECEGSPAARLSAPALPAHWP

GQRQLGHVGPNHRHGRPRPGPCRWPDGAR ADGTAGTL (SEQ ID NO:296),  
 PGSTPLASFKILALESADGHGGCSAGNDI (SEQ ID NO:297), GERDDQQVF  
 IQKVVPASQLFVRL (SEQ ID NO:298), RSVDGSPTTAFTVLECEGSPAARLS  
 (SEQ ID NO:299), PALPAHWPGQRQLGHVGPNHRHGRPR (SEQ ID NO:300),  
 5 PFIPRRPWPEPGVPTGIREAPESPRTRASQGIMAAALFKKEVSLSFILGGVVRG  
 VPRPLEGHGAGVGGRRRSGLRTSSWQRSTKLPPRRRRASACGGLGLPRWP  
 DKEVLLEAEWRLVREMRGEGGLGRQPHEGAERSRRGQLTVFQLFHQLLLRQATC  
 RGLA EAVHGGG (SEQ ID NO:301), PGVPTGIREAPESPRTRASQGIMAAALF  
 KKEV (SEQ ID NO:302), FILGGVRGVPRPLEGHGAGVGGRRRSGLP (SEQ ID  
 10 NO:303), GLPRWPDKEVLLEAEWRLVREMRG (SEQ ID NO:304), and/or GAER  
 SRRGQLTVFQLFHQLLLRQ (SEQ ID NO:305). Polynucleotides encoding these  
 polypeptides are also encompassed by the invention.

This gene is expressed primarily in human fetal kidney, and to a lesser extent, in  
 thymus and bone marrow cell line (RS4;11).

15 Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions which include, but are  
 not limited to, developmental, metabolic, immune or hematopoietic disorders.  
 Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
 20 providing immunological probes for differential identification of the tissue(s) or cell  
 type(s). For a number of disorders of the above tissues or cells, particularly of the  
 immune system, expression of this gene at significantly higher or lower levels may be  
 routinely detected in certain tissues or cell types (e.g., developmental, metabolic,  
 immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g.,  
 25 lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another  
 tissue or cell sample taken from an individual having such a disorder, relative to the  
 standard gene expression level, i.e., the expression level in healthy tissue or bodily  
 fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
 30 NO:129 as residues: Thr-17 to Trp-26, Pro-54 to Trp-61, Ala-65 to Arg-74, Pro-142 to  
 Leu-147, Pro-158 to Ala-165.

The tissue distribution in thymus and bone marrow cell lines indicates  
 polynucleotides and polypeptides corresponding to this gene are useful for the  
 diagnosis, treatment, and/or prevention of immune disorders involving stem cells.  
 35 Moreover, polynucleotides and polypeptides corresponding to this gene are useful for  
 the treatment and diagnosis of hematopoietic related disorders such as anemia,  
 pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are

important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the expression within fetal kidney indicates that this gene or gene product could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Moreover, the expression within fetal tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:15 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1002 of SEQ ID NO:15, b is an integer of 15 to 1016, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 6

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: HASAHASAHASGCGA (SEQ ID NO:306), QGVGVADGG

LERQRVDAGARLGHMGQPVAFSTRQLHLALPAPGTAGVTVPHPHAREGVV  
 GDLPLVPDAEDPTVGVPAGEGLVLGHVVERAELILVRGLHQAEALARESEEMH  
 GSRHG (SEQ ID NO:307), EGGLERQRVDAGARLGHMGQPVAFS (SEQ ID  
 NO:308), LALPAPGTAGVTVPHPHAREGVVGDPLV (SEQ ID NO:309), PAEG  
 5 LLVLGHVVERAELILVRGLHQAEA (SEQ ID NO:310), HLFKFFYTIAFMQWF  
 TEFMELFLSVWELIKTXNLCFVCFSEHKPGQLVPAGPTSQLLCRALGRVH  
 LCSPTTRSQTPTQSWVTPQLLWRLGSGRLVAQVLQVGSFCGPRVGDAVLGEQT  
 FQPFDLL (SEQ ID NO:311), AFMQWTFEFMELFLSVWELIKTXNLCFVC (SEQ  
 ID NO:312), and/or RSQTPTQSWVTPQLLWRLGSGRLVAQ (SEQ ID NO:313).

- 10 Polynucleotides encoding these polypeptides are also encompassed by the invention.  
 The gene encoding the disclosed cDNA is believed to reside on chromosome 16.  
 Accordingly, polynucleotides related to this invention are useful as a marker in linkage  
 analysis for chromosome 16.

- 15 This gene is expressed primarily in human infant brain, and to a lesser extent, in  
 adult brain and lung.

- Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions which include, but are  
 not limited to, neural, developmental, or pulmonary disorders. Similarly, polypeptides  
 20 and antibodies directed to these polypeptides are useful in providing immunological  
 probes for differential identification of the tissue(s) or cell type(s). For a number of  
 disorders of the above tissues or cells, particularly of the central nervous system  
 (CNS), expression of this gene at significantly higher or lower levels may be routinely  
 detected in certain tissues or cell types (e.g., neural, developmental, pulmonary, and  
 25 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,  
 amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken  
 from an individual having such a disorder, relative to the standard gene expression  
 level, i.e., the expression level in healthy tissue or bodily fluid from an individual not  
 having the disorder.

- 30 Preferred epitopes include those comprising a sequence shown in SEQ ID  
 NO:130 as residues: Ser-47 to Pro-57, Ser-77 to Glu-82, Thr-90 to Trp-98, Arg-124 to  
 Lys-137, Ala-183 to Glu-192, Lys-220 to Gln-229, Asn-244 to Arg-258, Thr-271 to  
 Asn-278, Glu-285 to Gly-297.

- The tissue distribution in infant and adult brain indicates polynucleotides and  
 35 polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or  
 prevention of diseases of the CNS, such as mental retardation, schizophrenia,  
 Alzheimer's disease, paranoia, depression, and mania. Moreover, polynucleotides and

polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral  
5 neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, dementia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain  
10 indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. The protein product of this gene may also show utility in the detection, treatment, and/or prevention of a variety of pulmonary disorders, particularly those related to disorders of the mucosal or endothelial tissues. The  
15 expression within fetal tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in  
20 cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
25 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:16 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more  
30 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1225 of SEQ ID NO:16, b is an integer of 15 to 1239, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.

35

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 7



The gene encoding the disclosed cDNA is believed to reside on chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17. In specific embodiments, polypeptides of the invention

5 comprise the following amino acid sequence:

GAWGVEVVAVGSKAGCLVYQLCDLKQITFFFRASVCLSV (SEQ ID NO:314),  
 PASLGSSWGQKLRRGGTRKSFQELSPSSAPPACLPQPPASTWLSSWPRPPCW  
 PPMCSWALGXCFPATGQWLPTSCCLWWCPDAGGRQKHFRSRWXTSWETW  
 QPYLTGLISSVLRAXRPDSYLQFRSLXQXXLCCAFVIALGGGCFLLTALYLER  
 10 DETRAWQXVTGTPDSNDVSDNDLERQGLLSGXGASTEER (SEQ ID NO:315), L  
 RGGTRKSFQELSPSSAPPACLPQP (SEQ ID NO:316), ATGQWLPTSCCLW  
 WCPDAGGRQKHFRSR (SEQ ID NO:317), GGCFLLTALYLERDETRAWQXV  
 (SEQ ID NO:318), APHLRLQPACHSPLPLGSRPGPDHPAGLLCVPGPWG  
 ASVLQLGSGCRHPAVCGGAQMPGDGRSTSDHGGXHPGXPGSPISQDLSLVSC  
 15 GPXALTPICSASAXXXXXCAAPLSSPWGAAASC (SEQ ID NO:319),  
 PACHSPLPLGSRPGPDHPAGLLCV (SEQ ID NO:320), and/or  
 SGCRHPAVCGGAQMPGDGRSTSDHGG (SEQ ID NO:321). Polynucleotides  
 encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in pineal gland and thymus.

20 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, endocrine, emotional or behavior disorders, in addition to autoimmune diseases. Similarly, polypeptides and antibodies directed to these

25 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, endocrine, hematopoietic, neural, and cancerous and wounded tissues) or bodily fluids

30 (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
 35 NO:131 as residues: Asp-18 to Gln-27, Arg-44 to Asn-49.

The tissue distribution in thymus indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of

immune and autoimmune diseases, such as lupus, neutropenia, transplant rejection, and inflammatory diseases. Moreover, the expression within pineal gland indicates the protein product of this gene may be useful in disorders associated with biological clock aberrations, emotional distress, lethargy, or metabolic conditions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1391 of SEQ ID NO:17, b is an integer of 15 to 1405, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 8

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When tested against K562 cell lines, supernatants removed from cells containing this gene activated the ISRE (interferon-sensitive responsive element ) promoter element. Thus, it is likely that this gene activates leukemia cells, or more generally, immune or hematopoietic cells, through the JAK-STAT signal transduction pathway. ISRE is a promoter element found upstream in many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

GLKVMEICSLTFLEATNLQSRCQQAMLPLKALRKNPFLLLPSFDGCCQSLA  
 FPGLWLQHSNLCLNHMTFLVYLLCVSVFKYFFPFSCITYTSHWI (SEQ ID  
 NO:322), ICSLTFLEATNLQSRCQQAMLP (SEQ ID NO:323), and/or GLWLQHS  
 NLCLNHMTFLVYLLCVSV (SEQ ID NO:324). Polynucleotides encoding these  
 polypeptides are also encompassed by the invention.

This gene is expressed primarily in IL-1 and LPS induced neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly inflammation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:132 as residues: Ser-45 to His-50, His-52 to Ile-57, Lys-67 to His-81.

The tissue distribution in neutrophils, combined with the detected ISRE biological activity indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of inflammatory disorders, such as psoriasis, inflammatory bowel disease, rheumatoid arthritis, and sepsis. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1520 of SEQ ID NO:18, b is an integer of 15 to 1534, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 9

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: PFPLLPPKRRGLLYHLIQKSTLGLVVWFREHLDSRSQ (SEQ ID NO:325), RGXPSWPMHTLVYAQHSTTHTPLIQPQWTQVIDQPPGITHQFCVR XCXCPTLESCVQECVTRSRXKPTTGVPGPQRLA (SEQ ID NO:326), TPLIQPQW TQVIDQPPGITHQFCV (SEQ ID NO:327), ALGPSQTCDLDVWLVAKPSFFRGPQ GIHYFSLWRRKPLSHWVSIWQLQGQETMPAMLRSPAGQATVATGPPRGSPS PQDLPSYHRKQVESSHRHSWEPASQSQ (SEQ ID NO:328), CDLDVWLVAKPSF FRGPQGIHYFSLWRR (SEQ ID NO:329), and/or AGQATVATGPPRGSPSPQDLP SYHRKQV (SEQ ID NO:330). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in synovial fibroblasts, and to a lesser extent, in endothelial cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, skeletal or vascular disorders, particularly arthritis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal, vascular, endothelial, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in synovial fibroblasts indicates polynucleotides and polypeptides corresponding to this gene are useful for treatment of arthritis. Moreover, polynucleotides and polypeptides corresponding to this gene are useful in the detection

and treatment of disorders and conditions afflicting the skeletal system, in particular osteoporosis, bone cancer, as well as, disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). The protein product of this gene may also be useful for the detection, treatment, and/or prevention of a variety of vascular disorders which include, but are not limited to, atherosclerosis, embolism, stroke, microvascular disease, or aneurysm. The protein may also be useful in the treatment of integumentary disorders, particularly those related to aberrations in the extracellular matrix or lamina. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1219 of SEQ ID NO:19, b is an integer of 15 to 1233, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 10

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

XGDTXTQNSRHDTPLIDYYRESCTLQYRPEFPGRPTRPRGSCPQYPGPAIPRT  
 SWALGEGDAAPRGAHH PRRADVPLG (SEQ ID NO:331), YRESCTLQYRPEFPG  
 RPTRPRGSCPQYPGP (SEQ ID NO:332), GKLYAAVPSGIPGSTHASARLMPPVS  
 RSSYSEDIVGSRRRRRSSSGSPSPQSRCSSWDGCSRSHSRGREGXRPPWSEL  
 DVGALYPFSRSGSRGRLPRFRNYAFASSWSTSYSGYRYHRALLCRRTAVSGR  
 LREGREPSAEEAEGEREDWGIGSA (SEQ ID NO:333), SGIPGSTHASARLMPP

VSRSSYS (SEQ ID NO:334), GCSRSHSRGREGXRPPWSELDVGALYPFS (SEQ ID NO:335), TAVSGRLREGREPSAEEAEGEREDW (SEQ ID NO:336), RIRKAA VQIPTRKNIGXRRPVVQETRKKERISRLKESIGNILIVTVTQSLTQILTLMMI KRELKPRRKRRKRNTKQXKRRIRKPKKNPVTQAVKTQKRTCQKLPGMEQ  
 5 PNVADTMDLIGPEAPINTYLFKMKNL (SEQ ID NO:337), TRKKERISRLKESIGNILIVTVTQSLTQ (SEQ ID NO:338), and/or VKTQKRTCQKLPGMEQPNVA DTMDLIGP (SEQ ID NO:339). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 6. Accordingly, polynucleotides related to this invention are  
 10 useful as a marker in linkage analysis for chromosome 6.

This gene is expressed primarily in retina.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are  
 15 not limited to, visual disorders, particularly retinopathy. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the ocular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell  
 20 types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, vitreous humor, aqueous humor, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 The tissue distribution in retina indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of diseases of the retina, for example, diabetic retinopathy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

35 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1076 of SEQ ID NO:20, b is an integer of 15

to 1090, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.

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## FEATURES OF PROTEIN ENCODED BY GENE NO: 11

When tested against NIH3T3 cell lines, supernatants removed from cells containing this gene activated the EGR1 (early growth response gene 1) promoter element. Thus, it is likely that this gene activates fibroblast cells, or more generally, other cells of the integumentary system, through the EGR1 signal transduction pathway. EGR1 is a separate signal transduction pathway from Jak-STAT. Genes containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

LPFTLKPKMKIPFSSRLINNNLQYIDCILSLKRCEEILLMWHGLLLCLASVFLE  
LRGDRPPLLASLLEPHKMPLHSSSL (SEQ ID NO:340), LKPKMKIPFSSRLIN  
NNLQYIDC (SEQ ID NO:341), SLKRCEEILLMWHGLLLCLASVF (SEQ ID  
NO:342), LRGDRPPLLASLLEPHKMPLH (SEQ ID NO:343), LQMHTGSGFKGK  
SCEVAFYVAQAEKPGEGAYLHGAQETQKQIEADHATLRGSPHSVSKTKYNLY  
IANYYLLAWRKMES (SEQ ID NO:344), CEVAFYVAQAEKPGEGAYLH (SEQ ID  
NO:345), and/or ATLRGSPHSVSKTKYNLYIANYY (SEQ ID NO:346).  
Polynucleotides encoding these polypeptides are also encompassed by the invention.

25 This gene is expressed primarily in human ovarian cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive disorders, particularly cancers, such as ovarian cancer.

30 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the female reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual

35 having such a disorder, relative to the standard gene expression level, i.e., the

expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in human ovarian cancer tissue indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of ovarian cancer. Moreover, the expression within cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:21 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 668 of SEQ ID NO:21, b is an integer of 15 to 682, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.

## 25 FEATURES OF PROTEIN ENCODED BY GENE NO: 12

Contact of cells with supernatant expressing the product of this gene increases the permeability of the plasma membrane of myeloid leukemia cells to calcium. Thus, it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of immune or hematopoietic cells, in addition to other cells or cell types. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating myeloid cells. Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium and sodium, as well as alter pH and membrane potential. Alterations in small molecule concentration can be measured to identify supernatants which bind to receptors of a particular cell. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:



LSASLLDRYPASESNNYIFNFVLYMLHFLAGTLFSLFPDFELSPRSATLFPDLR  
 TVQLLSSRPHL (SEQ ID NO:347), LLDRYPASESNNYIFNFVLYMLH (SEQ ID  
 NO:348), FPDFELSPRSATLFPDLRTV (SEQ ID NO:349), NGGFYDVSKQAG  
 LIEFLCIIFYPMAHVICGSRFTIVRTIPVHYVGEYFIKSSIWILYRINERTATKK  
 5 AASDFQKNFRCLDAF (SEQ ID NO:350), KQAGLIEFLCIIFYPMAH (SEQ ID  
 NO:351), and/or YFIKSSIWILYRINERTATKKAA (SEQ ID NO:352).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in anergic T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 10 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions which include, but are  
 not limited to, immune or hematopoietic disorders, particularly immunodeficiencies and  
 inflammatory disorders. Similarly, polypeptides and antibodies directed to these  
 polypeptides are useful in providing immunological probes for differential identification  
 15 of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,  
 particularly of the immune system, expression of this gene at significantly higher or  
 lower levels may be routinely detected in certain tissues or cell types (e.g., immune,  
 hematopoietic cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum,  
 plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken  
 20 from an individual having such a disorder, relative to the standard gene expression  
 level, i.e., the expression level in healthy tissue or bodily fluid from an individual not  
 having the disorder.

The tissue distribution in anergic T-cells, combined with the detected calcium  
 flux biological activity, indicates polynucleotides and polypeptides corresponding to  
 25 this gene are useful for the diagnosis and treatment of immune disorders, particularly  
 those involving anergic T-cells. Moreover, the secreted protein can also be used to  
 determine biological activity, to raise antibodies, as tissue markers, to isolate cognate  
 ligands or receptors, to identify agents that modulate their interactions, and as  
 nutritional supplements. It may also have a very wide range of biological activities.  
 30 Typical of these are cytokine, cell proliferation/differentiation modulating activity or  
 induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for  
 treating human immunodeficiency virus infection, cancer, autoimmune diseases and  
 allergy); regulation of hematopoiesis (e.g. for treating anaemia or as adjunct to  
 chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or  
 35 nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for  
 control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections,  
 tumors); hemostatic or thrombolytic activity (e.g. for treating haemophilia, cardiac

infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behaviour. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies  
5 directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:22 and may have been publicly available prior to conception of the present  
10 invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 756 of SEQ ID NO:22, b is an integer of 15 to  
15 770, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 13

20

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: SPRXGRXFXTSRKQISGFLEFD (SEQ ID NO:353). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in bone marrow.

25

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly leukemia or multiple myeloma. Similarly, polypeptides and antibodies directed to these polypeptides are  
30 useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,  
35 synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the

expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in bone marrow tissue indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of some types of leukemia, and other disorders involving bone marrow tissues or cells. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:23 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 551 of SEQ ID NO:23, b is an integer of 15 to 565, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.

### 30 FEATURES OF PROTEIN ENCODED BY GENE NO: 14

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: MKHAAFGLIPLVKEIYRYLKI KSKLLIGSGKCQLQPEWL QTSLINSSLLMDWLTPY (SEQ ID NO:354), IYRYLKI KSKLLIGSGKCQLQPE WLQTS (SEQ ID NO:355), QLGLPWDQSKGPRKNGLSMCGSVYSTIWSLIA SRREETIRVIVLYIQSPNINTRHISKRGLNKALTNP (SEQ ID NO:356), SKGPR

KNGLSMCGSVYSTIWS (SEQ ID NO:357), and/or QSPNINTRHISKRGLNK (SEQ ID NO:358). Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 This gene is expressed primarily in adult retina, and to a lesser extent, in 12 week old early stage human.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, visual or developmental disorders, particularly retinopathy. Similarly,  
10 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the ocular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., visual, developmental cancerous and wounded  
15 tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, aqueous humor, vitreous humor, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 The tissue distribution in human retina indicates polynucleotides and polypeptides corresponding to this gene are useful for treatment of retinopathy, and other disorders involving the visual system. Moreover, the expression within embryonic tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other  
25 proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:24 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

35 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1342 of SEQ ID NO:24, b is an integer of 15

to 1356, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 15

The translation product of this gene has homology to the conserved human non-differentiated blood cell tyrosine kinase receptor fragment (See Genbank Accession No. R76466) which is thought to be important in signalling essential cellular pathways. In  
 10 specific embodiments, polypeptides of the invention comprise the following amino acid sequence: HPQTSAGGFPLHQGLPTVS (SEQ ID NO:359), PSWFPELSPWPLKTL  
 KKRRQMRLRRRGRLCRLSPATTTTADTCRCPARSYRGSGRRPACAQDSPAPPS  
 RPTRRAWKCALRPKRAAQWSTGVPPSPRSSTTGCCFGTAAXCAEGARR  
 (SEQ ID NO:360), TTTADTCRCPARSYRGSGRRPA (SEQ ID NO:361), and/or  
 15 PSRPTRRAWKCALRPKRAAQWST (SEQ ID NO:362). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human fetal epithelium.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
 20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental, integumentary, immune, or hematopoietic disorders, particularly skin cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,  
 25 particularly of the integumental system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, integumentary, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having  
 30 such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:139 as residues: Gln-26 to Ala-39, Cys-48 to His-55.

The tissue distribution in human fetal epithelium, combined with the homology  
 35 to a conserved tyrosine kinase receptor, indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of skin cancer, or other disorders related to the integument, particularly proliferative

conditions. Similarly, polynucleotides and polypeptides corresponding to this gene are useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various connective tissue disorders such as arthritis, trauma, tendonitis, chondromalacia and inflammation, autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (ie. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:25 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 603 of SEQ ID NO:25, b is an integer of 15 to 617, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.

### 35 FEATURES OF PROTEIN ENCODED BY GENE NO: 16

When tested against PC12 cell lines, supernatants removed from cells containing this gene activated the EGR1 (early growth response gene 1) pathway. Thus, it is likely that this gene activates sensory neuron cells, or generally other cells or cell types, particularly immune cells, through the EGR1 signal transduction pathway. EGR1 is a separate signal transduction pathway from Jak-STAT, genes containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

ARGVLNLRNRFECFSIIETV (SEQ ID NO:363), IGQLVMKSICHFQRLLSVAI  
DFASQFLKNYIFSSTHSSKAGFSVVCSLPKWLYTDGMEMVLKITHKLSF (SEQ  
ID NO:364), and/or QRLLSVAIDFASQFLKNYIFSSTH (SEQ ID NO:365).

Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 8. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 8.

This gene is expressed primarily in fetal liver, and to a lesser extent, in resting T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, hematopoietic, or hepatic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, hepatic, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal liver and resting T-cells, combined with the detected EGR1 biological activity indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of immune disorders involving T-cells, and more generally, hematopoietic conditions. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia.

pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Additionally, expression within fetal tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:26 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 634 of SEQ ID NO:26, b is an integer of 15 to 648, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 17

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: LMKTASRMLLLE (SEQ ID NO:366). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in CD34-positive T cells from cord blood, and to a lesser extent, in anergic T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a



biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly in immune system maturation and hematopoietic development. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:141 as residues: Ile-46 to Tyr-56.

The tissue distribution in CD34-positive T cells and anergic T cells indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of diseases involving hematopoietic development and stem cell maturation, including protection of stem cells from chemotherapy, immunosuppression during transplant rejection, and neutropenia. Moreover, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lens tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1374 of SEQ ID NO:27, b is an integer of 15 to 1388, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 18

When tested against U937 and Jurket cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) pathway. Thus, it is likely that this gene activates myeloid and T-cells, or more generally cells of immune or hematopoietic origin, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ATXWDXPGRNSARGERLHVGDAPW (SEQ ID NO:367), ARDER REVLKTLMLSTQRPQAFLPSQSWFVRLQKAGEGALKQENSLTIQNCLLCL PRVHRQRPTPPQPRGNTASVLQTSTEHLPRAAVLLVPNSCSPGXPTXLLSS (SEQ ID NO:368), ERREVLKTLMLSTQRPQAFLP (SEQ ID NO:369), GALKQEN SLTIQNCLLCLPRVHRQR (SEQ ID NO:370), and/or SVLQTSTEHLPRAAVLLVP NS (SEQ ID NO:371). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in activated human neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, such as neutropenia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing

immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:142 as residues: Val-25 to Gly-33.

The tissue distribution in activated neutrophils, combined with the detected GAS biological activity, indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of immune disorders involving neutrophils. Moreover, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of

a-b, where a is any integer between 1 to 602 of SEQ ID NO:28, b is an integer of 15 to 616, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 19

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ALVISNPLL (SEQ ID NO:372), PYINTQMCVSSRNKFCISG  
 10 HQKYDSHGRETFRFEMHKARASSWKNILKIRSLKIISRGFEITNA (SEQ ID NO:373), KFCISGHQKYDSHGRETFRFEMHKARAS (SEQ ID NO:374), HTLLEI ANPLQAAVLGASSIHTSTHLMFMGLKWTELHHSPDSVQGAGAAEAAQTR HSLRPGRGRERHDCTLKNLTLFIIC (SEQ ID NO:375), NPLQAAVLGASSIHP SIHTSTH (SEQ ID NO:376), and/or SLRPGRGRERHDCTLKN (SEQ ID NO:377).  
 15 Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are  
 20 not limited to, immune or hematopoietic disorders, such as neutropenia, inflammatory, or allergic conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or  
 25 lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
 30 individual not having the disorder.

The tissue distribution in neutrophils indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of immune disorders involving neutrophils, or more generally, immune or hematopoietic disorders. Moreover, the expression of this gene product indicates a role in the  
 35 regulation of the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other

processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma,

5 immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue

10 injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show

15 utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the

20 scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 814 of SEQ ID NO:29, b is an integer of 15 to 828, where both a and b correspond to the positions of nucleotide residues shown in

25 SEQ ID NO:29, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 20

30 This gene is expressed primarily in 7 week old early stage human. Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, fetal or developmental abnormalities, particularly congenital defects,

35 including metabolic conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,

particularly of the developmental systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in 7 week old early stage human tissue indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of fetal abnormalities. Expression within embryonic tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Furthermore, the protein is useful in the diagnosis, prevention, and/or treatment of various metabolic disorders such as Tay-Sachs disease, phenylketonuria, galactosemia, hyperlipidemias, porphyrias, leukemias, or Hurler's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 567 of SEQ ID NO:30, b is an integer of 15 to 581, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 21

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

AENVHCTPAWETGRDSEDGKGREGMGRDRKGWDGTGLDGTGWEGKRERNV

PA (SEQ ID NO:378), GRDSEDGKGREGMGRDRKGWDGTGLD (SEQ ID NO:379), TSLGDLWDYNNSSH (SEQ ID NO:380), DRRIIRTREAAVAVSRERP LHSSLGNRERLRRWEGTGRDGKGQEGMGRDGTGWDGMGREERKKCPS (SEQ ID NO:381), RPLHSSLGNRERLRRWEGTGRDGKG (SEQ ID NO:382),  
 5 NQSWGPMGL (SEQ ID NO:383), GGGGCSEPRTSIALQPGKQGETPKMGRD GKGWEGTGRDGTGRDWMGRDGKGREKEMSQQ (SEQ ID NO:384), KQGE TPKMGRDGKGWEGTGRDGTG (SEQ ID NO:385), and/or PVLGTYGTITTPV TELTKGQEKEGGVETVLYE (SEQ ID NO:386). Polynucleotides encoding these polypeptides are also encompassed by the invention.

10 This gene is expressed primarily in frontal cortex from a patient suffering from schizophrenia.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are  
 15 not limited to, neural disorders, such as Schizophrenia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain  
 20 tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 The tissue distribution in frontal cortex tissue indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of some central nervous system disorders, for example, schizophrenia. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioural disorders, or  
 30 inflammatory conditions such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning  
 35 disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural

function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 775 of SEQ ID NO:31, b is an integer of 15 to 789, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.

## 20 FEATURES OF PROTEIN ENCODED BY GENE NO: 22

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: KIVFIDQKWSK (SEQ ID NO:387), CSLFWGILFLSRLRIH LFLSLKPCMCLRPIDILSHFLDIFVTSVLSELEKSSLKTTETFSFAVFLLLMMN (SEQ ID NO:388), LSRLRIHLFLSLKPCMCLRPIDILSH (SEQ ID NO:389), and/or VLSELEKSSLKTTETFSFAVFL (SEQ ID NO:390). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in thymus and neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly inflammation, or disorders related to immune cell maturation and/or activation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain



tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:146 as residues: Lys-38 to Leu-46.

The tissue distribution in thymus and neutrophils indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of inflammatory disorders, such as psoriasis, inflammatory bowel disease, rheumatoid arthritis, and sepsis. Moreover, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:32 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 870 of SEQ ID NO:32, b is an integer of 15 to

884, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 23

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: TLFYILH (SEQ ID NO:391). Polynucleotides encoding these polypeptides are also encompassed by the invention.

10 This gene is expressed primarily in bone marrow.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and disorders afflicting blood cells. Similarly, polypeptides and  
15 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or  
20 bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
25 NO:147 as residues: Pro-30 to Asn-36.

The tissue distribution in bone marrow indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of diseases afflicting the blood, including leukemia, neutropenia, anemia, and stem cell protection during chemotherapy. Moreover, polynucleotides and  
30 polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or  
35 chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the

expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:33 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- 10 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 852 of SEQ ID NO:33, b is an integer of 15 to 866, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.

15

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 24

This gene is expressed primarily in Merkel cells.

- 20 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, integumentary disorders, particularly aberrations in mechanosensory function. Similarly, polypeptides and antibodies directed to these polypeptides are
- 25 useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly in tissues involved in sensory function, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., integumentary, sensory, and cancerous and wounded tissues) or bodily fluids (e.g.,
- 30 lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 35 The tissue distribution in Merkel cells indicates polynucleotides and polypeptides corresponding to this gene are useful for Merkel cell dysfunctions, which may include aberrations in sensory function. Alternatively, polynucleotides and polypeptides corresponding to this gene are useful for the treatment, diagnosis, and/or

prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma),  
5 injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to  
10 viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). Moreover, the protein product of this gene may also be useful for the treatment or diagnosis of various connective tissue disorders such as arthritis, trauma, tendonitis, chondromalacia and inflammation, autoimmune disorders such as  
15 rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets  
20 for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the  
25 scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1680 of SEQ ID NO:34, b is an integer of 15 to 1694, where both a and b correspond to the positions of nucleotide residues shown  
30 in SEQ ID NO:34, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 25

35 The translation product of this gene shares sequence homology with dihydropyridine receptor or nitrate transporter which are thought to be important in transport of small molecules across the cell membrane. In specific embodiments,

polypeptides of the invention comprise the following amino acid sequence:  
GTSFSVLSLIHDTG (SEQ ID NO:392). Polynucleotides encoding these polypeptides  
are also encompassed by the invention. The gene encoding the disclosed cDNA is  
believed to reside on chromosome 11. Accordingly, polynucleotides related to this  
5 invention are useful as a marker in linkage analysis for chromosome 11.

This gene is expressed primarily in kidney cortex and muscle tissue from a  
patient with multiple sclerosis, and to a lesser extent, in fetal liver/spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
10 biological sample and for diagnosis of diseases and conditions which include, but are  
not limited to, muscle, urogenital, or renal disorders, particularly musculodegenerative  
conditions such as multiple sclerosis, in addition to kidney or metabolic disorders and  
diseases. Similarly, polypeptides and antibodies directed to these polypeptides are  
useful in providing immunological probes for differential identification of the tissue(s)  
15 or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
the multiple sclerosis and renal system, expression of this gene at significantly higher or  
lower levels may be routinely detected in certain tissues or cell types (e.g., muscle,  
urogenital, renal, hepatic, metabolic, immune, hematopoietic, and cancerous and  
wounded tissues) or bodily fluids (e.g., lymph, serum, bile, amniotic fluid, plasma,  
20 urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an  
individual having such a disorder, relative to the standard gene expression level, i.e.,  
the expression level in healthy tissue or bodily fluid from an individual not having the  
disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
25 NO:149 as residues: Ala-66 to Leu-73.

The tissue distribution in kidney cortex and muscle tissue, combined with the  
homology to small molecule transporters indicates polynucleotides and polypeptides  
corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of  
disorders of renal functions and muscular diseases, including multiple sclerosis,  
30 muscular dystrophy, cardiomyopathy, fibroids, myomas, and rhabdomyosarcomas.  
The tissue distribution in kidney indicates that this gene or gene product could be used  
in the treatment and/or detection of kidney diseases including renal failure, nephritis,  
renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis,  
nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and  
35 kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney  
abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome.  
Protein, as well as, antibodies directed against the protein may show utility as a tumor

marker and/or immunotherapy targets for the above listed tissues. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological

5 activities. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons,

10 ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other

15 hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available

20 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more

25 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1201 of SEQ ID NO:35, b is an integer of 15 to 1215, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.

30

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 26

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

35 VLISASTIGSRTSGAQGMEKMTIPTLAVGEPKTPEKSKCSLKQCFSSCNVHIDH  
LGLLLKCKF (SEQ ID NO:393), ASTIGSRTSGAQGMEKMTIPTLA (SEQ ID

NO:394), and/or GEPKTPEKSKCSLKQCFSSCNVHIDHL (SEQ ID NO:395).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in kidney medulla.

Therefore, polynucleotides and polypeptides of the invention are useful as  
5 reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions which include, but are  
not limited to, renal, urogenital, or more generally, disorders afflicting endothelial  
tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful  
in providing immunological probes for differential identification of the tissue(s) or cell  
10 type(s). For a number of disorders of the above tissues or cells, particularly of the renal  
system, expression of this gene at significantly higher or lower levels may be routinely  
detected in certain tissues or cell types (e.g., renal, urogenital, endothelial, and  
cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,  
synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual  
15 having such a disorder, relative to the standard gene expression level, i.e., the  
expression level in healthy tissue or bodily fluid from an individual not having the  
disorder.

The tissue distribution in kidney medulla indicates polynucleotides and  
polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or  
20 prevention of renal disorders, including lesions, vascular diseases, hydronephrosis,  
and renal diseases associated with systemic disorders. Moreover, the gene or gene  
product could be used in the treatment and/or detection of kidney diseases including  
renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema,  
pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome,  
25 glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's  
Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney,  
polycystic kidney, and Falconi's syndrome. The protein product can also be used for  
the treatment, detection, and/or prevention of various endothelial disorders, which  
include microvascular disease, embolism, aneurysm, stroke, or atherosclerosis.  
30 Protein, as well as, antibodies directed against the protein may show utility as a tumor  
marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
and accessible through sequence databases. Some of these sequences are related to SEQ  
ID NO:36 and may have been publicly available prior to conception of the present  
35 invention. Preferably, such related polynucleotides are specifically excluded from the  
scope of the present invention. To list every related sequence is cumbersome.  
Accordingly, preferably excluded from the present invention are one or more

polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1780 of SEQ ID NO:36, b is an integer of 15 to 1794, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 27

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

10 RIRSQDLAIMTTCFKKYEFSSFFVLGFLRRWGATLCLGFTSFAIKFHPSSLCSEKE  
 GKDFSGFALSIGHPERKKKEEGWARWLTPVVPVLWEAEVGGSPPEVSS (SEQ ID  
 NO:396), TTCFKKYEFSSFFVLGFLRRWGA (SEQ ID NO:397), SEKEGKDFSGF  
 ALSIGHPERKKKEEGW (SEQ ID NO:398), MNECIAKPCMAAFSCSPSCCLPSR  
 15 PGCSREQRCAFSCEPCHTVEHWVEPMGQQRQEHTQGSVLPSSHPSRGKATT  
 VHSCCQEPWG (SEQ ID NO:399), FCSCPSCLPSRPGCSREQRCAFSCEP (SEQ  
 ID NO:400), GQRQEHTQGSVLPSSHPSRGKAT (SEQ ID NO:401), GVVNSCLL  
 PLPPRLATGMDCGGFASRRMGGRQHAALSVFLPLPLAHGLYPMFNCVAGLT  
 GKGTSLLSGAARPAGEAAARAGTKGSHARFGNAFIHSF HSFIECLLNTYCV  
 20 SSALTAVGIGDILKNKNDKSSCLCSC (SEQ ID NO:402), GMDCGGFASRRMG  
 GRQHAALSVFLP (SEQ ID NO:403), LTGKGTSLLSGAARPAGEAAARAGT (SEQ  
 ID NO:404), and/or LNTYCVPSALTAVGIGDILKN (SEQ ID NO:405).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal lung.

25 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pulmonary or developmental disorders and/or diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing

30 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the pulmonary system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., pulmonary, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, pulmonary surfactant

35 or sputum, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression



level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal lung indicates polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of diseases related to pulmonary functions and infections. Moreover, the expression within fetal tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1160 of SEQ ID NO:37, b is an integer of 15 to 1174, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.

## 25 FEATURES OF PROTEIN ENCODED BY GENE NO: 28

This gene is expressed primarily in hepatocellular tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic or hepatic disorders or diseases, particularly hepatocellular tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., metabolic, hepatic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, bile, plasma, urine, synovial fluid and

spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in hepatocellular tumors indicates polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of hepatic disorders, particularly proliferative conditions such as hepatocellular tumors. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition, the protein may play a role in the treatment, detection, and/or prevention of developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of  $a-b$ , where  $a$  is any integer between 1 to 1073 of SEQ ID NO:38,  $b$  is an integer of 15 to 1087, where both  $a$  and  $b$  correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where  $b$  is greater than or equal to  $a + 14$ .

## FEATURES OF PROTEIN ENCODED BY GENE NO: 29

The translation product of this gene has homology to a contains a helix-loop-helix motif from a *Caenorhabditis elegans* protein (See Genbank Accession No. gil1326280) which is thought to function as a modulator of gene expression. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

TSLSQLWHFCHFVWPVKFCCGGCPVHCRMFSISGLYLLNASAPSLQLNDPKCL  
QT (SEQ ID NO:406), and/or WPVKFCCGGCPVHCRMFSISGLYLLNA (SEQ ID NO:407). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in normal breast.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, or endocrine disorders, particularly of the breast, such as breast cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cancer and metabolic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, endocrine, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, breast milk, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in breast indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of some types of breast cancer. The protein can also be used for the treatment, detection, and/or prevention of disorders related to ductile tissues or cell types, particularly secretory dysfunctions. The protein can also be used for the treatment of vascular disorders such as atherosclerosis, microvascular disease, embolism, stroke, or aneurysm. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 424 of SEQ ID NO:39, b is an integer of 15 to 438, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.

35

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 30

When tested against K562 cell lines, supernatants removed from cells containing this gene activated the ISRE (interferon-sensitive responsive element ) promoter element. Thus, it is likely that this gene activates leukemia cells, or potentially  
 5 other cells or cell-types, through the JAK-STAT signal transduction pathway. ISRE is a promoter element found upstream in many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the ISRE element, can be used to indicate proteins  
 10 involved in the proliferation and differentiation of cells. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:  
 SCRCWALGAGGGQRQWVGRS (SEQ ID NO:408), TGAQAPKMGARQKRPL  
 QTRIKNSSKSTLWPPQWVRCGRWWTWPSRKKTSRPRRQLFTSTLSTSASALV  
 WPVSWFSQEGH (SEQ ID NO:409), MGARQKRPLQTRIKNSSKSTLWPP (SEQ  
 15 ID NO:410), and/or PRRQLFTSTLSTSASALVWPVSW (SEQ ID NO:411).  
 Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human testes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
 20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive disorders, particularly abnormalities of the testes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive  
 25 system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, testicular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, seminal fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the  
 30 expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:154 as residues: Leu-26 to Glu-52, Gln-71 to Lys-79.

The tissue distribution in testes, combined with the detected ISRE biological  
 35 activity, indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of abnormalities of the testes, such as male infertility and proliferative conditions. and/or could be used as a male

contraceptive. The protein can also be used for the maintenance normal testicular function. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 720 of SEQ ID NO:40, b is an integer of 15 to 734, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.

15

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 31

This gene is expressed primarily in colon, and to a lesser extent, in thymus.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, gastrointestinal, immune, or hematopoietic disorders, particularly abnormalities of the colon, and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., gastrointestinal, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in colon and thymus tissue indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of abnormalities of the colon. The protein can also be used for treating inflammatory conditions, or potentially in modulating immune system activation in the treatment of gastrointestinal disorders. Protein, as well as, antibodies directed against

the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:41 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1332 of SEQ ID NO:41, b is an integer of 15 to 1346, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 32

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: DGGGKEEGVSCLKISLLCGPWLWLP (SEQ ID NO:412), HEMGELAICHTRVPFSLPSSAQGVQNLQGPIGHLAVCTPSSLTSWHFPQKREKW  
 20 STVNKRQRFLQFPAPLRNWIPQTPLSLSVSSGPLGSFTVFTLLSLCAWPWCCRD  
 CYKSCCPIPIFNLTAPLCVHTPEPSS (SEQ ID NO:413), SSAQGVQNLQGPIGHLAVCTPS (SEQ ID NO:414), VNKRQRFLQFPAPLRNWIPQTPLSLSVS (SEQ ID NO:415), CCRDCYKSCCPIPIFNLTAPLCV (SEQ ID NO:416), DLNVTNEGEGKE  
 25 VLGQGSTNNEKKCQKATSNTEPRAREAKARHANMGTSRESPTWSLTAE  
 GLKAKSKMQGKATKGAASTMGSHNQGPHKREIFKHETPSSFPPPSQCQPE  
 LLPYKYWATLASGYVPSWLPVSDSYRINTAIKDKNGQDT (SEQ ID NO:417),  
 VLGQGSTNNEKKCQKA TSNTEPRA (SEQ ID NO:418), RESPTWSLTAE  
 GLKAKSKMQGKATKGAAS (SEQ ID NO:419), and/or GYVPSWLPVSDSYRI  
 NTAIKDK (SEQ ID NO:420). Polynucleotides encoding these polypeptides are also  
 30 encompassed by the invention.

This gene is expressed primarily in rhabdomyosarcoma, and to a lesser extent in heart and thymus.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
 35 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, muscle disorders, particularly rhabdomyosarcoma and other proliferative conditions. Similarly, polypeptides and antibodies directed to these polypeptides are

useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the muscular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., muscle, and cancerous and  
5 wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
10 NO:156 as residues: Gly-28 to Asp-33.

The tissue distribution in rhabdomyosarcoma tissue indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of rhabdomyosarcoma. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of  
15 various muscle disorders, such as muscular dystrophy, cardiomyopathy, fibroids, or myomas. The protein can also be used for the amelioration of proliferative conditions in other tissues, including modulation of the immune response to such tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:42 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

25 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 984 of SEQ ID NO:42, b is an integer of 15 to 998, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.

30

### FEATURES OF PROTEIN ENCODED BY GENE NO: 33

In specific embodiments, polypeptides of the invention comprise the following  
35 amino acid sequence: NSAEQSMILILVT (SEQ ID NO:421), RXDRXPVPELPGYEPT  
RTDISSFKNYRYAFDFARDKDKQRSLDIDTAKSMLALLLGRTWPLFSVFYQYLE  
QSKYRVMNKDQWYNVLEFSRTVHADLSNYDEDGAWPVLLDEFVEWQKVRQT

S (SEQ ID NO:422), PTRTDISSFKNIYRYAFDFARDKDQRSL (SEQ ID NO:423), SMLALLLGRTWPLFSVFYQYLE QSKYRVM (SEQ ID NO:424), FSRTVHADLSN YDEDGAWPVLLDEFVE (SEQ ID NO:425), IYRYAFDFAR (SEQ ID NO:426), KD QRSLDI (SEQ ID NO:427), NVLEFSRT (SEQ ID NO:428), and/or DLSNYDEDGA  
5 WPVLLDEFVEW (SEQ ID NO:429). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 11.

10 This gene is expressed primarily in aortic endothelium, and to a lesser extent, in cancers.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endothelial disorders, particularly abnormalities of the vascular system  
15 and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endothelial, vascular, and  
20 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:157 as residues: Arg-22 to Lys-31.

The tissue distribution in aortic endothelium indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment, detection, and/or prevention of abnormalities of the vascular system (i.e. embolism, atherosclerosis,  
30 aneurysm, stroke, microvascular disease, etc.) and cancers. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ  
35 ID NO:43 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.



Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 644 of SEQ ID NO:43, b is an integer of 15 to 658, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 34

Polypeptides of the invention do not comprise the polypeptide sequence shown as Genbank Accession W59652, which is hereby incorporated herein by reference. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: LFRCPIGKAGTPAGXGPEFPGRPTRPVREKELTETFE (SEQ ID NO:430), FFVFPYPYPFRPLPIPFPRFPWFRNFIPIPIESAPTTPLPSEK (SEQ ID NO:432), PWFRNFIPIPIESAPTTPLP (SEQ ID NO:433), and/or GKAGTPAGXGPEFPGRPTRPV (SEQ ID NO:431). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in Hodgkin's lymphoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly Hodgkin's lymphoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:158 as residues: Ser-21 to Asp-35, Pro-47 to Pro-52, Pro-62 to Asn-67.

The tissue distribution in Hodgkin's lymphoma tissue indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of Hodgkin's lymphoma. Moreover, polynucleotides and

polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic-related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex- vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:44 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 552 of SEQ ID NO:44, b is an integer of 15 to 566, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 35

When tested against U937 and K562 cell lines, supernatants removed from cells containing this gene activated both the GAS (gamma activating sequence), and the ISRE (interferon-sensitive responsive element ) promoter elements. Thus, it is likely that this gene activates pro-myeloid, leukemic, or more generally, other cells or cell-types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. ISRE is a promoter element found upstream in many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a

large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. The translation product of this gene was shown to have

5 homology to a conserved trypsin inhibitor which is thought to play an essential role in protein metabolism and regulation (See Genbank Accession No. pirlS35098IS35098). In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

FYPMTQGKESLPLLALQIFNTTFRPSFAFFSGHRTLFFGVRSNPPKPRIFLIW

10 LIAVAL (SEQ ID NO:434), LLALQIFNTTFRPSFAFFSGHRTLFFGVRS (SEQ ID NO:435), HLAQTVMMHPQKSFYQVKNTNHS DRGAIEETQILEDRLGQIPLCLES QIWEA (SEQ ID NO:436), KNTNHS DRGAIEET QILEDRLGQIPLCL (SEQ ID NO:437), QGCYRRDS NIGRQVRPDSIMLRKPD LGSITHYGSVLGNLNYCDLP QLYRNPSLGNSGMREMFSPFYNPVECHP (SEQ ID NO:438), PDSIMLRKPD

15 LGSITHYGSVLGN (SEQ ID NO:439), and/or YRNPSLGNSGMREMFSPFYNPV (SEQ ID NO:440). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in brain frontal cortex.

Therefore, polynucleotides and polypeptides of the invention are useful as

20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural disorders, particularly disorders of the central nervous system or endocrine system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the

25 tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system or endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample

30 taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain frontal cortex, combined with the detected GAS and ISRE biological activities indicates polynucleotides and polypeptides corresponding

35 to this gene are useful for diagnosis or treatment of disorders of the central nervous system, caused by trauma, inflammation, demyelination, neoplasia, and degenerative diseases. Additionally, the molecule may function as a neuropeptide or hormone.

Moreover, considering the homology to a trypsin inhibitor and its localization in the brain, indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:45 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1263 of SEQ ID NO:45, b is an integer of 15 to 1277, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 36

30

The translation product of this gene was found to have homology to a zinc finger protein from *Mus musculus* (See Genbank Accession No. gnllPIDle225687) which is thought to be involved in the modulation of gene regulation. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: NSARGLSGGHPPFWLSEGHPPF (SEQ ID NO:441), TDSDLTLGILLGLI YTNHIWEMFLAASRINSPKLEPEKSVKRQINFPSKDVGCSLEVPKDGPPL SHGKEWIPLSHRKGWIPLSHMKGWPSLSHGKGWPP LSPRAEF (SEQ ID

NO:442), LGILLLLGIYTNHIWEMFLAA (SEQ ID NO:443), KSVKRQINFPSSKDV  
GCSLEVPKDGPP (SEQ ID NO:444), GKEWIPLSHRKGWIPLSHMKGWPSLSH  
(SEQ ID NO:445), GWASTQPRERMDPAQPQERMDPSQPHERMALTQPWKRMALP  
TQPSCRI (SEQ ID NO:446), and/or PAQPQERMDPSQPHERMALTQPWK (SEQ ID  
5 NO:447). Polynucleotides encoding these polypeptides are also encompassed by the  
invention.

This gene is expressed primarily in neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
reagents for differential identification of the tissue(s) or cell type(s) present in a  
10 biological sample and for diagnosis of diseases and conditions which include, but are  
not limited to, immune or hematopoietic disorders. Similarly, polypeptides and  
antibodies directed to these polypeptides are useful in providing immunological probes  
for differential identification of the tissue(s) or cell type(s). For a number of disorders  
of the above tissues or cells, particularly of the immune system, expression of this gene  
15 at significantly higher or lower levels may be routinely detected in certain tissues or cell  
types (e.g., immune, hematopoietic cancerous and wounded tissues) or bodily fluids  
(e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or  
cell sample taken from an individual having such a disorder, relative to the standard  
gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
20 individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
NO:160 as residues: Ser-30 to Asp-39.

The tissue distribution in neutrophils indicates polynucleotides and polypeptides  
corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of  
25 immune disorders involving neutrophils, including neutropenia. The expression of this  
gene product indicates a role in regulating the proliferation; survival; differentiation;  
and/or activation of hematopoietic cell lineages, including blood stem cells. This gene  
product may be involved in the regulation of cytokine production, antigen presentation,  
or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by  
30 boosting immune responses). Since the gene is expressed in cells of lymphoid origin,  
the natural gene product may be involved in immune functions. Therefore it may be also  
used as an agent for immunological disorders including arthritis, asthma,  
immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis,  
granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia,  
35 neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune  
reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-  
host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue

injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The protein product of this gene can be used in the preparation of therapeutic compositions, for treating, preventing or delaying the recurrence of a tumour or neuronal disorders, e.g. genetic diseases or acquired degenerative encephalopathies such as Alzheimer's disease. Moreover, the protein is also useful in the induction or inhibition of cellular apoptosis resulting in inhibition of tumour cell growth, to suppress tumour formation, to induce G1 arrest of the cell cycle and to act as nuclear transcription factor. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:46 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 428 of SEQ ID NO:46, b is an integer of 15 to 442, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 37

When tested against U937 and K562 cell lines, supernatants removed from cells containing this gene activated both the GAS (gamma activating sequence), and the ISRE (interferon-sensitive responsive element ) promoter elements. Thus, it is likely that this gene activates pro-myeloid, leukemic, or more generally, other cells or cell-types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. ISRE is a promoter element found upstream in

many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. The protein product of this gene was found to have homology to the G-protein coupled receptor TM1 long consensus polypeptide (See Genbank Accession No. R50790) which indicates the protein is useful in the modulation of signalling events, cell-cycle regulation and/or transcriptional regulation. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: IANGGGRPIKLNALYK IQNECKIVFTCIDF (SEQ ID NO:448), and/or MPCIK SKMNAKLFSLVLTLCMIPISVLFGTCI (SEQ ID NO:449). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in duodenum.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, gastrointestinal disorders, particularly abnormalities of the duodenum. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., gastrointestinal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in duodenum, the homology to the TM1 g-protein coupled receptor consensus sequence, in addition to the detected GAS and ISRE biological activities, indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of the abnormalities of the duodenum, particularly proliferative conditions such as cancers. Moreover, the protein can be used in G-protein coupled receptor ligand binding assays. The assay can be used to identify fragments from GPR proteins (see Genseq Accession Nos. R48686-R48758 for examples) which retain biological activity such as binding a GPR ligand or

modulating GPR ligand binding to a GPR (see Genseq Accession Nos. R48759-R48758, R50569-R50807 and R89189-R89195 for examples of polypeptide fragments). The polypeptide fragments can be used in compositions for treating subjects suffering from a pathology related to a GPR abnormality e.g. a psychotic disorder such as schizophrenia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:47 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 876 of SEQ ID NO:47, b is an integer of 15 to 890, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.

## 20 FEATURES OF PROTEIN ENCODED BY GENE NO: 38

The translation product of this gene shares sequence homology with a growth and transformation dependent protein (>gil207250), which is thought to be important in the regulation of cellular growth and proliferation. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

QVAMGSLSGRLAAGSCFRLCERDVSSSLRLTRSSDLKRINGFCTKPQESPG  
 APSRTYNRVPLHKPTDWQKKILIWSGRFKKEDEIPETVSLEMLDAAKNK (SEQ  
 ID NO:450), GLRLAAGSCFRLCERDVSSSLRLTR (SEQ ID NO:451), APSRTYNR  
 VPLHKPTDWQKK (SEQ ID NO:452), IWSGRFKKEDEIPETVSLEMLDA (SEQ ID  
 NO:453), MDFAQNHRKVPPELHPALTTECLYTNLRIGRKRSSYGQVASKRKM  
 KSQRLSRWRCLMLQRTCE (SEQ ID NO:454), KVPPELHPALTTECLYTNLR  
 (SEQ ID NO:455), KRSSYGQVASKRKMKSQRLSRWRCLM (SEQ ID NO:456),  
 INGCTKPQESP (SEQ ID NO:457), RVPLHKPTD (SEQ ID NO:458), WSGRFK  
 KE (SEQ ID NO:459), EMLDAAKNK (SEQ ID NO:460), SYLMIALTV (SEQ ID  
 NO:461), and/or MVIEGKAA (SEQ ID NO:462). Polynucleotides encoding these  
 polypeptides are also encompassed by the invention.



This gene is expressed primarily in ovary.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, or endocrine disorders, particularly abnormalities of the ovary. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, endocrine, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:162 as residues: Lys-25 to Thr-33, Leu-39 to Glu-47.

The tissue distribution in ovary, combined with the homology to the growth and transformation dependent protein, indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of the abnormalities of the ovary such as ovarian cancer. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:48 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 723 of SEQ ID NO:48, b is an integer of 15 to 737, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 39

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: RPGMRALGSCLSLALCSPQARPGPRTLDASTATLTPHF  
 5 SPCARFSPVGPSAVPFAATPLPLAGHPQ (SEQ ID NO:463), GSCLSLALCS  
 PQARPGPRT (SEQ ID NO:464), HFSPCARFSPVGPSAVPFAATPL (SEQ ID  
 NO:465), AIEERNKSRLTQQASEPTGSPRYLHEQHPGSRSQMDGSLTMXCPPP  
 RVRDDRTSARGVPRQAAPDIVGGRPSSRACVSXPACAPSAAVFPY (SEQ ID  
 NO:466), LTQQASEPTGSPRYLHEQHPGSR (SEQ ID NO:467), and/or SARG  
 10 VPRQAAPDIVGGRPSSRACVS (SEQ ID NO:468). Polynucleotides encoding these  
 polypeptides are also encompassed by the invention.

This gene is expressed primarily in ovarian tumor.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 15 biological sample and for diagnosis of diseases and conditions which include, but are  
 not limited to, reproductive or endocrine disorders, particularly ovarian tumors.  
 Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
 providing immunological probes for differential identification of the tissue(s) or cell  
 type(s). For a number of disorders of the above tissues or cells, particularly of the  
 20 female reproductive system, expression of this gene at significantly higher or lower  
 levels may be routinely detected in certain tissues or cell types (e.g., reproductive,  
 endocrine cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum,  
 plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken  
 from an individual having such a disorder, relative to the standard gene expression  
 25 level, i.e., the expression level in healthy tissue or bodily fluid from an individual not  
 having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
 NO:163 as residues: Met-1 to Gly-6, Trp-23 to Arg-29, Ala-38 to Ser-45.

The tissue distribution in ovarian tumor tissue indicates polynucleotides and  
 30 polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or  
 prevention of reproductive disorders, particularly ovarian conditions, such as tumors.  
 Protein, as well as, antibodies directed against the protein may show utility as a tumor  
 marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
 35 and accessible through sequence databases. Some of these sequences are related to SEQ  
 ID NO:49 and may have been publicly available prior to conception of the present  
 invention. Preferably, such related polynucleotides are specifically excluded from the

- scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 557 of SEQ ID NO:49, b is an integer of 15 to 571, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 40

10

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: PRVRKTPHLSASGK (SEQ ID NO:469), YYYSMLKICHITI LETLSDRTPRKFAK KCYILYIKLSDSSVEKVAYTLLLLIPAAIEKK (SEQ ID NO:470), and/or TILETLSDRTPRKFAK KCYILYIKLSDSSVEK (SEQ ID NO:471).

- 15 Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in endometrial stromal cells treated with estradiol.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive disorders, particularly cancer of the endometrium. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, endometrial, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:164 as residues: Met-1 to Ser-7.

- 35 The tissue distribution in endometrial stromal cells indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of diseases of the endometrium, particularly cancer or diseases caused by hormonal imbalances. Protein, as well as, antibodies directed against the protein may

show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:50 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 342 of SEQ ID NO:50, b is an integer of 15 to 356, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where b is greater than or equal to a + 14.

#### 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 41

The translation product of this gene shares sequence homology with the smaller hepatocellular oncoprotein which is thought to be important in protein synthesis leading to cellular transformation. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: VHTKEIFRERSAGFPVK (SEQ ID NO:472), LEMGFQPTKEINARGSEPCQAQSTSLPKLPRWGSRPEAPQTPQGG LESRCCTPVSKQSLNLKADRFKALTLGRAQWLT PVIQALSELRWVDHLRSGV (SEQ ID NO:473), FQPT KEINARGSEPCQAQSTSLPK (SEQ ID NO:474), PKLPR WGSRPEAPQTPQGGLESRCCTP (SEQ ID NO:475), and/or RFKALTLGRAQWLT PVIQALSELRWVD (SEQ ID NO:476). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human bladder.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, urogenital disorders, particularly proliferative conditions, such as bladder tumors. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the bladder, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., urogenital, bladder, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal

fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
5 NO:165 as residues: Pro-30 to Lys-38, Pro-45 to Ile-60, Leu-79 to Ser-96, His-98 to Gly-118.

The tissue distribution in bladder tumors indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis of carcinomas and preneoplastic or pathological conditions of bladder, or of the urogenital/renal system.  
10 Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:51 and may have been publicly available prior to conception of the present  
15 invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 899 of SEQ ID NO:51, b is an integer of 15 to  
20 913, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 42

25

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: RIPLQSDGSFLHEKSSQQRSNRNFPCPTLQCNPEVSFWFV  
VTDPSKNHTLP AVEVQSAIRMNKNRINNAFFLNDQTLEFLKIPSTLAPMDPS  
VPIWIIIFGVIFCIIIV AIALLLSGIWQRRRKNKEPSEVDDAEDKCENMITIENGIP  
30 SDPLDMKG GHINDAFMTEDERLTPL (SEQ ID NO:477), PCPTLQCNPEVSF  
WFVVTDP SKNHT (SEQ ID NO:478), AIRMNKNRINNAFFLNDQTLEFL (SEQ ID  
NO:479), IWQRRRKNKEPSEVDDAEDKCENM (SEQ ID NO:480), PLDMKG  
GHINDAFMTEDER (SEQ ID NO:481), GSRTTALQRGVSLSSVMKASLICPP  
FMSRGSEGMPFSIVIMFSLSSASSTSDGSLFLLRCQIPDKISSAIATMM  
35 MQNITPNIIIQMGTDGSMGGASVEGIFKNSRVWSFRKKALLIRFLFILMADCTST  
A GRV (SEQ ID NO:482), VSLSSVMKASLICPPFMSRGSEGMPFS (SEQ ID

NO:483), and/or SMGGASVEGIFKNSRVWSFRKKAL (SEQ ID NO:484).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in kidney, and to a lesser extent, in gall bladder and testes.

- 5 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the renal, urogenital, or reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing
- 10 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the renal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., renal, urogenital, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, seminal fluid, synovial
- 15 fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:166 as residues: Lys-60 to Ala-66, Thr-78 to Ser-83.

- 20 The tissue distribution in kidney indicates the protein product of this gene could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital
- 25 kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Moreover, the tissue distribution in gall bladder indicates that the protein is useful for the treatment, detection, and/or prevention of various metabolic disorders. Alternatively, the expression within testes indicates that the protein is useful in normal testicular function. Therefore, this gene product may be useful in the treatment of male
- 30 infertility, and/or could be used as a male contraceptive. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ
- 35 ID NO:52 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1342 of SEQ ID NO:52, b is an integer of 15 to 1356, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 43

10 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: GARGSQDAPALQEA E V R G P E R A Q P A R G R (SEQ ID NO:485), S E R P G E G P A R P G Q D D Q G P A V P A V A G A G V G V H D P A D H R V L G Q R S A A H F Y L H T S F S R P H T G P P L P T P G P D R T G S S R P T M S T S F W T I S H A G V K Q S D L P R K E T E Q P P A P G E H G G E R E R L R L V P A R R P A Q P R P G P A A G G A E E R A A G L L R Q L Q P

15 G L P H Q G A R I R R H P Q L G A E P P D R G R P A R G H L L L R A Q G G L H Q L E A R D D R A E R K P A A P R C A L P R P A A H P A R A R A Q R Q R A P D L Q Q V L A P L R E A L P P P H E G Q A Q E V H Q V P L R A R P L R A P D L R L P Q Q V R A G E R G V L P Q V R R A H A A G V R Q P H Q P A R L G A R G L P R W P Q G V L R Q L H P V P A G P A H G E A G A L Q R A L A A G V P P L P P V P D R L R F L G K L E T L D E D A A Q L L Q L L Q V D R Q S A S P R A T G T G P P A A G R R T G S P R S P W P G G

20 S S C I N S T R P T L F S S A T P S P K T S S E T E S F R V A F S R V P G T (SEQ ID NO:486), R P G Q D D Q G P A V P A V A G A G V G V H D P A (SEQ ID NO:487), S R P H T G P P L P T P G P D R T G S S R (SEQ ID NO:488), S H A G V K Q S D L P R K E T E Q P P A P G E (SEQ ID NO:489), R R P A Q P R P G P A A G G A E E R A A G L L (SEQ ID NO:490), R R H P Q L G A E P P D R G R P A R G H L L L (SEQ ID NO:491), R D D R A E R K P A A P R C A L P R P A A H P A R (SEQ ID NO:492), R A P D L Q Q V L A P L R E A L P P P H E G Q A Q E V (SEQ ID NO:493), D L R L P Q Q V R A G E R G V L P Q V R R A H A A G (SEQ ID NO:494), Q P A R L G A R G L P R W P Q G V L R Q L H P V P A G (SEQ ID NO:495), A G V P P L P P V P D R L R F L G K L E T L D E (SEQ ID NO:496), Q L L Q L L Q V D R Q S A S P R A T G T G P P A A (SEQ ID NO:497), N S T R P T L F S S A T P S P K T S S E T E S F R (SEQ ID NO:498), L G G K R T A G P P G V A A A A A R R P R P E

30 S P A S P G I V V D L A R V A E A V H L P P V L V E G R Q L L R V R V Q Q V L D E V G E G H L E A S A E G L A R R G G Q A G V V G V H P Q H G H G E L A V E L L V L Q L E L A A E G G D Q A H E G V A H E E E L G V L L E L D L H E V A G E L P V A A P E L V E G Q V R A G V V H V L A R D A Q R V A V G R T A V Q Q A S A Q H D H A L P V G A G H L G H V A V D G P V P V V H D Q V A Q L R V G D V V E C A L L G G E G Q A G V G A E A P Q H V P P L R L L P A L V W A A P G V A R G P V V A S H A L L H A P P A

35 Q A A A P S P F W E G H S A S R Q H E K L S R N S S T S E S A V S S L S C P A R A W A A A A P C A A (SEQ ID NO:499), E A V H L P P V L V E G R Q L L R V R V Q Q V (SEQ ID NO:500), G H L E A S A E G L A R R G G Q A G V V G V H P (SEQ ID NO:501), Q L E L A A E G G D Q A H E G V A H E

EELGVLEL (SEQ ID NO:502), GELPVAAPELVEGQVRAGVVHVLARDA (SEQ ID NO:503), AVQQASAQHDHHALPVGAGHLGHVA (SEQ ID NO:504), ALVW AAPGVARGPVVASHALLHA (SEQ ID NO:506), HDQVAQLRVGDVVECALLG GEGQAG (SEQ ID NO:505), PPAQAAAPSPFWEGHSASRQHEKLSRNS (SEQ ID NO:507), SRVTFPERRRSSRLRRGSMEESVRGYDWSPRDARRSPDQGRQAE RRNVLRGFCANSSLAFTKERAFDDIPNSELSHLIVDDRHGAIYCYVPKV ACTNWKRVMIVLSGSLLRGAPYRDPLRIPREHVHNASAHLTNKFWRRYGK LSRHLMKVKLKKYTKFLFVRDPFVRLISAFRSKFELENEEFYRKFAVPMLRVY ANHTSLPASAREAFRAGLKVSFANFIQYLLDPHTEKLAPFNEHWRQVYRLC HPCQIDYDSWGSWRLWTRTPRSCCSYSRWTGSPLPELPEQDRQQLGGGLVR QD PPGLEAAAV (SEQ ID NO:508), RSPDQGRQQAERRNVLRGFCANSSLA (SEQ ID NO:509), TKERAFDDIPNSELSHLIVDDRHGAIYC (SEQ ID NO:510), FNKFWRRYGKLSRHLMKVKLKKY (SEQ ID NO:511), FVRLISAFRSKFELE NEEFYRKFA (SEQ ID NO:512), TSLPASAREAFRAGLKVSFANFIQYL (SEQ ID NO:513), and/or SYSRWTGSPLPELPEQDRQQLGGG (SEQ ID NO:514).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 7.

Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

It has been discovered that this gene is expressed primarily in PMA activated monocytic HL60 cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: blood related disease such as leukemia. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:167 as residues: Ala-29 to Thr-37, Pro-39 to Leu-63.

The tissue distribution in HL60 cells suggests the protein product of this clone is useful for the diagnosis, treatment, and/or prevention of blood related diseases such



as leukemia. Moreover, the protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:53 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1533 of SEQ ID NO:53, b is an integer of 15 to 1547, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.

## 25 FEATURES OF PROTEIN ENCODED BY GENE NO: 44

When tested against fibroblast cell lines, supernatants removed from cells containing this gene activated the EGR1 (early growth response gene 1) promoter element. Thus, it is likely that this gene activates fibroblasts, or more generally, other cells or cell types, through the EGR1 signal transduction pathway. EGR1 is a separate signal transduction pathway from Jak-STAT, genes containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. The gene encoding the disclosed cDNA is believed to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: STGCSE (SEQ ID NO:515),

CLCLGCGLPELHSYLDPGPYLLVYPTLFWLCPSAVSPWAYTCYQLGLGPQWGA  
 AALSFTVDAAIRVWDVSTETCVLPWFRRGGVTNCSGPQTAAKSWLPLLQLSF  
 ESGRPRCGLVRGGLLYQGAVRLAA GAQMAADCCSLYWESH (SEQ ID  
 NO:516), YPTLFWLCPSAVSPWAYTCYQLGLGP (SEQ ID NO:517), DVSTETCV  
 5 LPWFRGGGTNCSGPQ (SEQ ID NO:518), LLYQGAVRLAA GAQMAADCCSL  
 (SEQ ID NO:519), NKRKTYLFLFVGMWGVGQNRWWPWERVPRGRGWGCL  
 SKEGQVMNRASTPSRGFLGPPKHWAKTWKLGIDKVQRDVGNSACGPAH  
 TEQGPFVEGRWKVMSWGWAPGSPWIMPQGRSSNTGLFRVRKRRMTGLPS  
 CTLGFPFISTARRSPLGSQTME (SEQ ID NO:520), GVGQNRWWPWERVPRG  
 10 RGWGCLSKEG (SEQ ID NO:521), AKTWKLGIDKVQRDVGNSACGPAHTE  
 (SEQ ID NO:522), and/or WAPGSPWIMPQGRSSNTGLFRVRKRRMTGLPSC  
 TLGFPFIST (SEQ ID NO:523). Polynucleotides encoding these polypeptides are also  
 encompassed by the invention.

This gene is expressed primarily in fetal tissues such as fetal brain, fetal liver,  
 15 fetal kidney, and to a lesser extent, in T cells and macrophages.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions which include, but are  
 not limited to, blood-related, immuno-related, neural-related, or developmental  
 20 disorders. Similarly, polypeptides and antibodies directed to these polypeptides are  
 useful in providing immunological probes for differential identification of the tissue(s)  
 or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
 the hematopoiesis and immune system, expression of this gene at significantly higher or  
 lower levels may be routinely detected in certain tissues or cell types (e.g., neural,  
 25 immune, hematopoietic, urogenital, renal, hepatic, metabolic, developmental, and  
 cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, amniotic fluid,  
 bile, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from  
 an individual having such a disorder, relative to the standard gene expression level, i.e.,  
 the expression level in healthy tissue or bodily fluid from an individual not having the  
 30 disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
 NO:168 as residues: Cys-126 to Thr-138, Glu-165 to Gly-172, Thr-189 to Leu-200,  
 Gly-222 to Gly-229, Pro-346 to Lys-354.

The tissue distribution in fetal liver indicates polynucleotides and polypeptides  
 35 corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of  
 blood related diseases, particularly immune or hematopoietic disorders. Alternatively,  
 the expression within fetal brain indicates polynucleotides and polypeptides

corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Alternatively, the expression within fetal kidney indicates the protein product of this gene could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Moreover, the expression within various fetal tissues, combined with the detected EGR1 biological activity, indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:54 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1324 of SEQ ID NO:54, b is an integer of 15 to 1338, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 45**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: SSYQCPKVTFKSSVDT (SEQ ID NO:524). Polynucleotides  
5 encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 15. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 15.

This gene is expressed primarily in glioblastoma, liver, fetal lung, and  
10 amygdala.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural, metabolic, or developmental disorders, particularly mental or  
15 neurodegenerative conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g.,  
20 neural, metabolic, developmental, pulmonary, hepatic, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, amniotic fluid, pulmonart surfactant or sputum, bile, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
25 individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:169 as residues: Pro-31 to Ala-37, Lys-62 to Asn-72.

The tissue distribution in glioblastoma and amygdala indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment,  
30 and/or prevention of central nervous system disorders. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating  
35 diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder,

learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. The protein may also be useful in the treatment, detection, and/or prevention of liver disorders, which include, but are not limited to hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells. In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:55 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2057 of SEQ ID NO:55, b is an integer of 15 to 2071, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.

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#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 46**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: YIYSYLGFFNQINK (SEQ ID NO:525). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed in only T-cell helper II cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly infectious diseases, inflammatory, or immunodeficiency conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for

differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:170 as residues: Pro-44 to Tyr-49.

The tissue distribution in T-helper cells indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment of infectious diseases. Moreover, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:56 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more

polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1885 of SEQ ID NO:56, b is an integer of 15 to 1899, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 47

The translation product of this gene has been shown to have homology to the human nuclear factor IV (See Genbank Accession No. gi35038), which is thought to play a role as a type 2 DNA helicase in DNA metabolism either during transcription, DNA repair, and/or during the cell-cycle. Moreover, the protein may play a role in chromosomal translocations. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ARDLIL (SEQ ID NO:526), LTFYL QFLAPKDKPSGDTAAVFEEGGDVDDL VSTFNMHLVFCD (SEQ ID NO:527), and/or FLAPKDKPSGDTAAVFEEGGDVDDL (SEQ ID NO:528). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 2. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 2.

This gene is expressed primarily in activate T-cells, and to a lesser extent, in B-cells and monocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune or hematopoietic disorders, particularly leukemia, Grave's disease, rheumatoid arthritis and other autoimmune diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:171 as residues: Gly-27 to Cys-35.

The tissue distribution in T-cells, B-cells, and monocytes indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment or diagnosis of immune system diseases. Moreover, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:57 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1529 of SEQ ID NO:57, b is an integer of 15 to 1543, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.



## FEATURES OF PROTEIN ENCODED BY GENE NO: 48

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ARAGAKILFEGEF (SEQ ID NO:529), NFEIHSAPPFMLFVA  
 5 CLLHSSCPRTARFLASPLSESNVIFYQNQYQFPCILCFIEFARLTSFKHLIHSQSH  
 LVRLQYEDFSVSSE AWDTELT (SEQ ID NO:530), FPFMLFVACLLHSSCPRTA  
 RFLASPL (SEQ ID NO:531), NVIFYQNQYQFPCILCFIEFARLTSF (SEQ ID  
 NO:532), and/or SQSHLVRLQYEDFSVSSE AWDTE (SEQ ID NO:533).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

- 10 The gene encoding the disclosed cDNA is believed to reside on chromosome 14.  
 Accordingly, polynucleotides related to this invention are useful as a marker in linkage  
 analysis for chromosome 14.

This gene is expressed primarily in fetal tissues such as fetal liver, fetal brain,  
 fetal lung and fetal spleen.

- 15 Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions which include, but are  
 not limited to, developmental disorders and cancers. Similarly, polypeptides and  
 antibodies directed to these polypeptides are useful in providing immunological probes  
 20 for differential identification of the tissue(s) or cell type(s). For a number of disorders  
 of the above tissues or cells, particularly of the immune system and nervous system,  
 expression of this gene at significantly higher or lower levels may be routinely detected  
 in certain tissues or cell types (e.g., developmental, hepatic, immune, hemaopoietic,  
 neural, pulmonary, and cancerous and wounded tissues) or bodily fluids (e.g., serum,  
 25 plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell  
 sample taken from an individual having such a disorder, relative to the standard gene  
 expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
 individual not having the disorder.

- Preferred epitopes include those comprising a sequence shown in SEQ ID  
 30 NO:172 as residues: Gly-37 to Asp-46, Ser-48 to Val-54.

- The tissue distribution in fetal tissues indicates polynucleotides and polypeptides  
 corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of  
 developmental disorders and cancers. Moreover, the expression within embryonic  
 tissue and other cellular sources marked by proliferating cells indicates that this protein  
 35 may play a role in the regulation of cellular division, and may show utility in the  
 diagnosis and treatment of cancer and other proliferative disorders. The protein is also  
 useful in the treatment, detection, and/or prevention of immune, hematopoietic,

pulmonary, or metabolic diseases, disorders, and/or conditions. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:58 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1119 of SEQ ID NO:58, b is an integer of 15 to 1133, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 49

20

The translation product of this gene was found to have homology to a 35kd pulmonary surfactant protein, as well as, a GABA-like receptor (See Genbank Accession Nos. P70663, and gil540271, respectively), the latter of which is thought to be important in neuronal function. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: QKFLCASDGD (SEQ ID NO:534), AEVPLRVRRRHGRPHGPGGRQLALGIPALRSLPGCVPRHHGC SPGYGCLHRRILCLPLILLVYKQRQAASNRAQELVRMDSNIQGIENPGF EASPPAQGIPEAKVRHPLSYVAQRQPSESGRHLLSEPSTPLSPPGPGDVFF PSLDPVPDSPNFVIXPXWGTVGCCGWVWGRCI (SEQ ID NO:535), GPGG RQLALGIPALRSLPGCVPRHHGC (SEQ ID NO:536), FEASPPAQGIPEAK VRHPLSYVAQR (SEQ ID NO:537), DMSLGMWQHQQWDMKMDTGPPSQAPD TGHGGETSPPWHALGSPVLPEAALLSDFLVPQWLWGQACLPTGHRHLPQLPP TSSF SEDLSTG (SEQ ID NO:538), PPSQAPDTGHGGETSPPWHALGS (SEQ ID NO:544), PVDRSSEKLLVGGSWGRWRWPVGRQAWPQSHCGTKRKSDRR AASGKTGEPSACHGGEVSPPCPVSGAWEG GPVSILSH (SEQ ID NO:539), PVDRSSEKLLVGGSWGRWRWPV (SEQ ID NO:540), TKRKSDRRAASG KTGEPSACHGGEV (SEQ ID NO:541). MTSKFGESGTGSRDGKKTSPGPG

GDRGVLGSESRCPDSEGCRWAT (SEQ ID NO:542), and/or SPGPGGDRGV LGSESRCPD (SEQ ID NO:543). Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 This gene is expressed primarily in hematopoiesis cells such as neutrophils, eosinophils and T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, blood diseases and/or immune diseases. Similarly, polypeptides and  
10 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and  
15 wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
20 NO:173 as residues: Ser-44 to Ala-63, Pro-89 to Gly-98, Pro-129 to Trp-137.

The tissue distribution in neutrophils, eosinophils, and T cells indicates polynucleotides and polypeptides corresponding to this gene are useful for treating and diagnosis blood related diseases. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic  
25 related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be  
30 used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The homology to a pulmonary surfactant protein indicates that the protein is useful in enhancing or inhibiting the efficacy of the  
35 immune response across mucosal barriers, such as within the gastrointestinal tract, the sinuses, and the lungs. Protein, as well as, antibodies directed against the protein may

show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:59 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1476 of SEQ ID NO:59, b is an integer of 15 to 1490, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 50

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates promyeloid cells, or more generally, other cells of the immune or central nervous system, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: HEVQPSYLPNSGLI (SEQ ID NO:545). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in the central nervous system, adult liver, adult heart, and infant brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural, cardiovascular, or metabolic conditions or disorders. Similarly,

polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely  
5 detected in certain tissues or cell types (e.g., neural, cardiovascular, developmental, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene  
10 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tissues of the CNS and infant brain, combined with the detected GAS biological activity indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment, diagnosis, and/or prevention of CNS disorders. Moreover, polynucleotides and polypeptides corresponding to this  
15 gene are useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction,  
20 aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene  
25 product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. The expression within fetal tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or  
30 apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
35 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:60 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the

scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1322 of SEQ ID NO:60, b is an integer of 15 to 1336, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 51

10

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: LRISVLCRETACNWSHHPLDSN (SEQ ID NO:546).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 18.

15 Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 18.

This gene is expressed in whole brain, embryos, fetal liver and fetal spleen, and melanocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural, immune, hematopoietic, or developmental disorders, particularly mental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, immune, hematopoietic, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:175 as residues: Pro-27 to Lys-42.

35 The tissue distribution in brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of mental or neurodegenerative disorders. Alternatively, the expression within fetal

liver/spleen indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include

5 bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors

10 of various blood lineages, and in the differentiation and/or proliferation of various cell types. The protein may also be useful for the treatment and/or detection of metabolic disorders, which include Tay-Sachs disease, phenylketonuria, galactosemia, hyperlipidemias, porphyrias, and Hurler's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy

15 targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:61 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the

20 scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1691 of SEQ ID NO:61, b is an integer of 15 to 1705, where both a and b correspond to the positions of nucleotide residues shown

25 in SEQ ID NO:61, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 52

30 When tested against U937 and fibroblast cell lines, supernatants removed from cells containing this gene activated both the GAS (gamma activating sequence) and EGR1 (early growth response gene 1) promoter elements. Thus, it is likely that this gene activates promyeloid cells, fibroblasts, or more generally, immune or

35 integumentary cells or cell-types, through the JAK-STAT and/or EGR1 signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells.

Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. EGR1 is a separate signal transduction pathway from Jak-STAT, genes containing the EGR1 promoter are induced in various tissues and cell types upon  
5 activation, leading the cells to undergo differentiation and proliferation. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: LTVTVRNPGSTHASGRPRRRSGVWARRGLVWQ (SEQ ID NO:547). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in endometrial stromal cells and fetal brain  
10 tissue, and to a lesser extent, in microvascular endothelial cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, neural, developmental, or vascular disorders, particularly  
15 vascular leak syndrome and inflammation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endothelium, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell  
20 types (e.g., reproductive, neural, developmental, vascular, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
25 NO:176 as residues: Pro-63 to Cys-72, Gly-88 to Cys-93.

The tissue distribution in endometrial stromal cells, infant brain, and microvascular endothelial cells, combined with the detected GAS and EGR1 biological activities, indicates polynucleotides and polypeptides corresponding to this gene are  
30 useful for the treatment of various vascular disorders, which include, but are not limited to vascular leak syndrome, microvascular disease, atherosclerosis, aneurysm, stroke, embolism and inflammation. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and  
35 treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could



again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:62 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1017 of SEQ ID NO:62, b is an integer of 15 to 1031, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 53**

Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of HUVEC cells to calcium. Thus, it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of both vascular endothelial cells, in addition to other cell-lines or tissue cell types. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating endothelial cells, or more generally, neural or immune cells. Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium and sodium, as well as alter pH and membrane potential. Alterations in small molecule concentration can be measured to identify supernatants which bind to receptors of a particular cell. This protein is homologous to members of the butyrophilin gene family which are thought to play a role in myelin sheath development, in addition to serving as a membrane-specific receptor for cytoplasmic vesicles to the apical plasma membrane. In specific embodiments, polypeptides of the invention comprise the sequence  
SAQFSVLGPSGPILAMVGEDADLPCHLFPTMSAETMELKW (SEQ ID NO:574).  
Polynucleotides encoding these polypeptides are also encompassed by the invention. In specific embodiments, polypeptides of the invention comprise the sequence  
TPCSAQFSVLGPSGPILAMVGEDADLPCHLFPTMSAET (SEQ ID NO:548),  
MELKWVSSSLRQVVNVYADGKEVEDRQSAPYRGRTSILRDGITAGKAALRIHN

VTASDSG (SEQ ID NO:549), LEVKG YEDGGIHL ECRSTGWYPQPQI (SEQ ID NO:550), MASSLAFLLLNFHVSLLL VQLLTPCSAQFSVLGPSGPILAMVGE DADLPCHLFPTMSAETMELK WVSSSLRQVVNVYADG (SEQ ID NO:551), RHEL SHNRKNGELLIDRLYSVGSDSPMGIPRDIIFTDGFYWNPKVKTLKDRHF

5 WQSIDENGKFPGFPSA QLSCLPPLGPAAHSLSSVFCAWTLWAHPGHGG (SEQ ID NO:552), LLIDRLYSVGSDSPMGIPRDIIFT (SEQ ID NO:553), NPKVKT LKDRHFWQSIDENGKFPGF (SEQ ID NO:554), LGPAAHSLSSVFCAWTLWA HPGH (SEQ ID NO:555). RLQHWVLIFTLEVKG YEDGGIHL ECRSTGWYPQP QIQWSNAKGENIPAVEAPVVADGVGLYEVAASVIMRGGSGEGVSCIIRNSLL

10 GLEKTASISIADPSSGAPSPGSQPWQGPCLSCCCFSPEPVTSCGDNRRK (SEQ ID NO:556), GGIHL ECRSTGWYPQPQIQWSNAKG (SEQ ID NO:557), PQIQWS NAKGENIPAVEAPVVADGVGL (SEQ ID NO:558), NIPAVEAPVVADGVGL YEVAASVIMRG (SEQ ID NO:559), SGAPSPGSQPWQGPCLSCCCFSPEPVT (SEQ ID NO:560), SSSICDHERRLRGGCILHHQKFPPRPGKDSQHFHRRP

15 FFRSAQPWIAALAGTLPILLLL LAGASYFLWRQQKEITALSSEIESEQEMKE MGYAATEREISLRESLQEELKRKKIQYLTRGESSSDTNKSA (SEQ ID NO:561), KDSQHFHRRPFFRSAQPWIAALAGTLPI (SEQ ID NO:562), EIESEQEMKE MGYAATEREISLRESLQE (SEQ ID NO:563), VNNMIAFYSARDSYVYPHFSG EEMLQMLHLVK (SEQ ID NO:564), TPCSAQFSVLGPSGPILAMVGEDADLP

20 CHLFPTMSAET (SEQ ID NO:565), KWVSSSLRQVVNVYADGKEVEDR (SEQ ID NO:566), RTSILRDGITAGKAALRIHNVASD (SEQ ID NO:567), CYFQDGDYF EKALVELKVAALGS (SEQ ID NO:568), GYEDGGIHL ECRSTGWYPQPQIQ (SEQ ID NO:569), NIPAVEAPVVADGVGLYEVAASV (SEQ ID NO:570), QQKEITALSS EIESEQEMKEM (SEQ ID NO:571), LRESLQEELKRKKIQYLTRGESS (SEQ ID

25 NO:572), and/or GEEMLQMLHLVK (SEQ ID NO:573). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 6. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 6.

This gene is expressed primarily in rhabdomyosarcoma, and to a lesser extent, in T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, muscle, immune, or neural disorders, particularly rhabdomyosarcoma, infectious diseases, or neurodegenerative conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders

of the above tissues or cells, particularly of the immune system expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., muscle, immune, neural, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:177 as residues: Ala-78 to Arg-94.

The tissue distribution in rhabdomyosarcoma, the detected calcium flux biological activity, combined with the homology to the butyrophilin gene family indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis or treatment of muscle disorders, which include, but are not limited to, muscular dystrophy, cardiomyopathy, fibroids, myomas, and/or rhabdomyosarcomas. Moreover, the homology to the butyrophilin protein indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. The protein may also show utility in the correction or amelioration of myelin sheath deficiencies in developing and mature neurons and neural-cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:63 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more

polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1575 of SEQ ID NO:63, b is an integer of 15 to 1589, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 54

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: PQGGLTLPSVWG (SEQ ID NO:575), GGPCHLWLLGPRRT QLPGRRASLPFRSQGELTQAFLLGLWKHQPALTQEQQVRAERRREA VRMEI PGLFFASLANWGLLYRTSQDFISPYLCAAPSTPHPPLGGP (SEQ ID NO:576), GPRRTQLPGRRASLPFRSQGELT (SEQ ID NO:577), QMPALTQEQQVRAER RREA VRMEI (SEQ ID NO:578), and/or ANWGLLYRTSQDFISPYLCAAPSTP (SEQ ID NO:579). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

This gene is expressed primarily in brain, and to a lesser extent, in testes tumor.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural, endocrine, or reproductive disorders, particularly depression and infertility disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, endocrine, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, seminal fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:178 as residues: Thr-26 to Glu-33.

The tissue distribution in brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of depression and

other endocrine-related disorders. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, 5 Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in 10 feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. The protein product may also be useful in the treatment, detection, and/or 15 prevention of a variety of reproductive disorders which include, but are not limited to, the treatment of male infertility, and/or could be used as a male contraceptive. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available 20 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:64 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more 25 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1074 of SEQ ID NO:64, b is an integer of 15 to 1088, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.

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#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 55**

The translation product of this gene was found to have homology to the conserved R166.2 protein from *Caenorhabditis elegans* (See Genbank Accession 35 No.gi1949849), which is thought to play an important role in the regulation of cellular function and processes. In specific embodiments, polypeptides of the invention comprise the sequence: LSFKDKSTYIESSTKVYDDMAFRYLSWILFPLL (SEQ ID

NO:580), CYAVYSLLYLEHKGWYSWVLSM (SEQ ID NO:590), LLTFGFITMTPQ  
 LFINYKLKSV AHL PWRMLT (SEQ ID NO:581), TYKALNTFIDDLFAFVIKMP  
 VMYRIGCLRD (SEQ ID NO:582), DVVFFIYLYQRWIYRVDPTRVNEFGMSGED  
 (SEQ ID NO:583), VAGIFPRLSFKDKSTYIESSTKVYDDMAFRYLSWILFPLL  
 5 CYA (SEQ ID NO:584), PWVAGIFPRLSFKDKSTYIESSTKVYDD (SEQ ID  
 NO:586), AGEDSCHPVLSVQPDVHDLGWQESSPAYPSRTSPRISSPRPKC  
 MMIWHSCTCPGSSSR SWAAMPSTVFCTWSTRAGTPGCSACSTASC (SEQ ID  
 NO:587), LSVQPDVHDLGWQESSPAYPSRTSPRISSP (SEQ ID NO:588), GSSSR  
 SWAAMPSTVFCTWSTRAGTP (SEQ ID NO:589), and/or WAAMPSTVFCTWS  
 10 TRAGTP (SEQ ID NO:585). Polynucleotides encoding these polypeptides are also  
 encompassed by the invention. The gene encoding the disclosed cDNA is believed to  
 reside on chromosome 19. Accordingly, polynucleotides related to this invention are  
 useful as a marker in linkage analysis for chromosome 19.

This gene is expressed primarily in colon, smooth muscle and fetal bone.

15 Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions which include, but are  
 not limited to, gastrointestinal or vascular disorders, and abnormal muscular-skeletal  
 development, including proliferative conditions such as cancer. Similarly, polypeptides  
 20 and antibodies directed to these polypeptides are useful in providing immunological  
 probes for differential identification of the tissue(s) or cell type(s). For a number of  
 disorders of the above tissues or cells, particularly of the immune and muscular-skeletal  
 system, expression of this gene at significantly higher or lower levels may be routinely  
 detected in certain tissues or cell types (e.g., gastrointestinal, muscle, skeletal, vascular,  
 25 developmental, and cancerous and wounded tissues) or bodily fluids (e.g., serum,  
 plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell  
 sample taken from an individual having such a disorder, relative to the standard gene  
 expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
 individual not having the disorder.

30 Preferred epitopes include those comprising a sequence shown in SEQ ID  
 NO:179 as residues: Ser-128 to Thr-133, Thr-158 to Thr-166, Leu-168 to Gly-175,  
 Ala-179 to Asp-196.

The tissue distribution in colon and fetal bone indicates polynucleotides and  
 polypeptides corresponding to this gene are useful for the treatment and diagnosis of  
 35 abnormal bone formation, and/or various proliferative conditions (e.g. tumors),  
 particularly of the gastrointestinal system. Moreover, the expression within smooth  
 muscle tissue indicates polynucleotides and polypeptides corresponding to this gene are

useful for the detection, treatment, and/or prevention of a variety of vascular disorders, which include, but are not limited to the following: embolism, atherosclerosis, microvascular disease, aneurysm, stroke, and vascular leak syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:65 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1242 of SEQ ID NO:65, b is an integer of 15 to 1256, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 56

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: LGEFLSSQCFLP (SEQ ID NO:591). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in brain frontal cortex.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neural disorders, particularly neurological or neurodegenerative disorders and diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:180 as residues: Ala-122 to Gly-128.

The tissue distribution in brain frontal cortex indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of some neurological diseases such as depression. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:66 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1588 of SEQ ID NO:66, b is an integer of 15 to 1602, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 57

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates pro-myeloid cells, or more generally, immune or hematopoietic cells, through the JAK-STAT signal transduction pathway. GAS is a



promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins  
5 involved in the proliferation and differentiation of cells. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:  
RSRRNRVAMGMWASLDALWE (SEQ ID NO:592), PRVRCQQRAEGGMGAG  
IGVGPSERTDIAVTPRGRSEGASVGVAPVHAEGAGGTGWPWGCGHRWTLCG  
RCR PRSVSSGPCCSFPGQCIFGRPS (SEQ ID NO:593), GGMGAGIGVGPSER  
10 TDIAVTPRGR (SEQ ID NO:594), GCGHRWTLCGRCCR PRSVSSGPCCSFP (SEQ  
ID NO:595), and/or KKHGF NQQTGLGFFTWKYNKNKNLV (SEQ ID NO:596).  
Polynucleotides encoding these polypeptides are also encompassed by the invention.  
The gene encoding the disclosed cDNA is believed to reside on chromosome 1.  
Accordingly, polynucleotides related to this invention are useful as a marker in linkage  
15 analysis for chromosome 1.

This gene is expressed primarily in synovial cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are  
20 not limited to, skeletal afflictions, particularly rheumatoid arthritis or autoimmune conditions. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may  
25 be routinely detected in certain tissues or cell types (e.g., skeletal, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

30 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:181 as residues: Gln-27 to Val-39, Glu-50 to Arg-56.

The restricted tissue distribution in synovium, combined with the detected GAS biological activity, indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of rheumatoid arthritis since synovial  
35 fibroblasts are associated with the synovium and cartilage. Moreover, polynucleotides and polypeptides corresponding to this gene are useful in the detection and treatment of disorders and conditions afflicting the skeletal system, in particular osteoporosis, bone

cancer, as well as, disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). The protein may also be useful in the modulation of the immune response to regions of inflammation, or in inhibiting or ameliorating autoimmune responses. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:67 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 924 of SEQ ID NO:67, b is an integer of 15 to 938, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 58

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates pro-myeloid cells, or more generally immune or hematopoietic cells, in addition to other cells or cell-types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: PKLLPCSPAEGHTSLGPELLPF (SEQ ID NO:597), ASLELXPS KSQLSTEWGFTWIVGLGMPSTALWTECTCTPFLVLLSHASGHFFWLSPLAS

LVIPPVTDRK (SEQ ID NO:598), WGFTWIVGLGMSPSTALWTECTCTPFLVL  
 LSH (SEQ ID NO:599), VAVGVCREDMGIDRSKMSPDVGIWAIYWSAAGY  
 WPLIGFPGTPTQQEPALHRVGVYLDRTGNVSFYSAVDGVHLHTFSCS  
 SVSRLRPFFLVESISIFSHSTSD (SEQ ID NO:600), ITDRSKMSPDVGIWAIYW  
 5 SAAGYWPLI (SEQ ID NO:601), and/or RGTGNVSFYSAVDGVHLHTFSCSSV  
 SRLRP (SEQ ID NO:602). Polynucleotides encoding these polypeptides are also  
 encompassed by the invention. The gene encoding the disclosed cDNA is believed to  
 reside on chromosome 7. Accordingly, polynucleotides related to this invention are  
 useful as a marker in linkage analysis for chromosome 7.

10 This gene is expressed primarily in fetal tissues, and to a lesser extent, in liver  
 cells.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 reagents for differential identification of the tissue(s) or cell type(s) present in a  
 biological sample and for diagnosis of diseases and conditions which include, but are  
 15 not limited to, developmental or liver diseases, such as hepatocellular carcinoma.  
 Similarly, polypeptides and antibodies directed to these polypeptides are useful in  
 providing immunological probes for differential identification of the tissue(s) or cell  
 type(s). For a number of disorders of the above tissues or cells, particularly of the  
 immune and hepatic systems, expression of this gene at significantly higher or lower  
 20 levels may be routinely detected in certain tissues or cell types (e.g., developmental,  
 hepatic, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., serum,  
 plasma, bile, breast milk, urine, synovial fluid and spinal fluid) or another tissue or cell  
 sample taken from an individual having such a disorder, relative to the standard gene  
 expression level, i.e., the expression level in healthy tissue or bodily fluid from an  
 25 individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID  
 NO:182 as residues: Pro-30 to Gln-37, Arg-39 to Ser-45, Arg-74 to Arg-85.

The tissue distribution in liver, combined with the detected GAS biological  
 activity indicates polynucleotides and polypeptides corresponding to this gene are useful  
 30 for the treatment or diagnosis of hepatic conditions such as hepatocellular carcinoma.  
 Moreover, the expression within embryonic tissue and other cellular sources marked by  
 proliferating cells indicates that this protein may play a role in the regulation of cellular  
 division, and may show utility in the diagnosis and treatment of cancer and other  
 proliferative disorders. Similarly, developmental tissues rely on decisions involving cell  
 35 differentiation and/or apoptosis in pattern formation. Thus this protein may also be  
 involved in apoptosis or tissue differentiation and could again be useful in cancer

therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:68 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1571 of SEQ ID NO:68, b is an integer of 15 to 1585, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 59

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: GTRGLQNH RTE (SEQ ID NO:603). Polynucleotides encoding these polypeptides are also encompassed by the invention.

20 This gene is expressed primarily in prostate, and to a lesser extent, in tonsil and fetal lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, immune, developmental, or pulmonary disorders and/or diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, immune, developmental, pulmonary, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, amniotic fluid, pulmonary surfactant or sputum, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:183 as residues: Lys-32 to Lys-38.

- The tissue distribution in prostate indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of cancers, particularly of the prostate. The expression within tonsils indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. The expression also indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Moreover, the expression within fetal tissue indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders.
- Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.
- Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:69 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1662 of SEQ ID NO:69, b is an integer of 15 to 1676, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 60

- In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ELSGLG (SEQ ID NO:604). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in the brain.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, central nervous system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for

differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:184 as residues: Tyr-15 to Lys-21, Pro-62 to Phe-68.

The tissue distribution in brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of CNS disorders (such as Parkinson's disease). Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:70 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1330 of SEQ ID NO:70, b is an integer of 15 to 1344, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 61**

5           The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

          This gene is expressed primarily in the brain.

          Therefore, polynucleotides and polypeptides of the invention are useful as  
10 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, CNS diseases, such as Alzheimers and Parkinson's disease. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a  
15 number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to  
20 the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

          Preferred epitopes include those comprising a sequence shown in SEQ ID NO:185 as residues: Asp-44 to Cys-53, Asp-56 to Lys-66, Ser-78 to Lys-84.

          The tissue distribution in brain tissue indicates polynucleotides and polypeptides  
25 corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of CNS diseases such as Alzheimers and Parkinson's disease. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Huntington's Disease, Tourette Syndrome,  
30 meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance,  
35 and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition,

homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
5 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:71 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more  
10 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1460 of SEQ ID NO:71, b is an integer of 15 to 1474, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.

15

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 62

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: MDDIKI (SEQ ID NO:605), NFCVSKNTFNRVKRPIKWVKIF  
20 ANDISCKRLISRIHKEILPFNNKKQPDFKVKKSRK (SEQ ID NO:606), FNRVKR PIKWVKIFANDISCKRLISRIHKE (SEQ ID NO:607), ETQMANKYMKRCSTL (SEQ ID NO:608), VIRELQVKATRRCHYTPIKWSKSKTLISSNADEYVEPTRTLI HCWWKCKIVQPLCKTAW (SEQ ID NO:609), and/or ATRRCHYTPIKWSKSKT LISSN (SEQ ID NO:610). Polynucleotides encoding these polypeptides are also  
25 encompassed by the invention.

This gene is expressed primarily in duodenum, and to a lesser extent, in brain frontal cortex.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
30 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, gastrointestinal, neural, or endocrine disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression  
35 of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., gastrointestinal, neural, endocrine, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal



fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in colon indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of some gastrointestinal disorders, particularly cancers. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:72 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1998 of SEQ ID NO:72, b is an integer of 15 to 2012, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 63

This gene is expressed primarily in bone marrow.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, leukemia, immune deficiency syndromes, and other immune related diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of diseases of bone marrow, such as leukemia, bone cancer and immune deficiency syndrome. Furthermore, the polypeptides or polynucleotides are also useful to enhance or protect proliferation, differentiation, and functional activation of hematopoietic progenitor cells (e.g., bone marrow cells), useful in treating cancer patients undergoing chemotherapy or patients undergoing bone marrow transplantation. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:73 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1253 of SEQ ID NO:73, b is an integer of 15 to 1267, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 64**

When tested against sensory neuron cell lines, supernatants removed from cells containing this gene activated the EGR1 assay. Thus, it is likely that this gene activates sensory neuronal cells through a signal transduction pathway. Early growth response 1 (EGR1) is a promoter associated with certain genes that induces various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation.

This gene is expressed primarily in the testes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive system-related diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., testes, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in testes indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of reproductive system-related diseases. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:74 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1734 of SEQ ID NO:74, b is an integer of 15 to 1748, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 65

This gene is expressed primarily in synovial fibroblasts.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, rheumatoid arthritis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The restricted tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of rheumatoid arthritis, since synovial fibroblasts are associated with the synovium and cartilage. In addition, the expression of this gene product in synovium indicates a role in the detection and treatment of disorders and conditions afflicting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma and dermatomyositis as well as dwarfism, spinal deformation, and

specific joint abnormalities as well as chondrodysplasias (ie. spondylocpiphysal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above  
5 listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:75 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the  
10 scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1556 of SEQ ID NO:75, b is an integer of 15 to 1570, where both a and b correspond to the positions of nucleotide residues shown  
15 in SEQ ID NO:75, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 66

20 This gene is expressed primarily in ovarian cancer, and to a lesser extent in fetal tissues such as fetal liver and fetal brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are  
25 not limited to, cancers, particularly of the ovary. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell  
30 types (e.g., ovary, fetal, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

35 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:190 as residues: Pro-28 to Gln-33.

The tissue distribution in ovarian cancer tissue indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of cancers; e.g., ovarian cancer, as well as other tissues where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:76 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 510 of SEQ ID NO:76, b is an integer of 15 to 524, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 67

This gene is expressed primarily in testes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, male reproductive or hormonal related disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., testes, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:191 as residues: Pro-68 to Asp-73, Gln-92 to Glu-107, Gln-120 to Lys-126.

The tissue distribution in testes indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of male

reproductive or hormonal disorders. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:77 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1292 of SEQ ID NO:77, b is an integer of 15 to 1306, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 68

When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in human tonsils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., tonsils, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune disorders. Expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:78 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more



polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1465 of SEQ ID NO:78, b is an integer of 15 to 1479, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to a + 14.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 69

This gene is expressed primarily in human thymus and six week old human  
10 embryo.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endocrine diseases and leukemia. Similarly, polypeptides and antibodies  
15 directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endocrine, immune, cancerous and wounded  
20 tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in thymus and developing embryonic tissues indicates  
25 that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of leukemia or other immune diseases, especially those which are involved in fetal development. Furthermore, the tissue distribution in thymus and developing embryonic tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of various endocrine  
30 disorders and cancers, particularly Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Protein, as well as, antibodies directed against the protein may show utility as a  
35 tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ

ID NO:79 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more

- 5 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1780 of SEQ ID NO:79, b is an integer of 15 to 1794, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to a + 14.

10

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 70.

This gene is expressed primarily in adult pulmonary tissue.

- 15 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the cardiopulmonary system including asthma, bronchitis, apnea, enlarged heart, arrhythmia, strokes and heart attacks. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes
- 20 for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the cardiopulmonary system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., pulmonary, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell
- 25 sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:194 as residues: Pro-27 to Leu-41.

- 30 The tissue distribution in pulmonary tissues indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment or diagnosis of diseases such as arrhythmia, apnea, asthma and possibly for the early detection and prevention of patients likely to have strokes or heart attacks. Furthermore, the tissue distribution in pulmonary tissues indicates polynucleotides and polypeptides
- 35 corresponding to this gene are useful for the detection and treatment of disorders associated with developing lungs, particularly in premature infants where the lungs are the last tissues to develop. Additionally, the tissue distribution indicates polynucleotides

and polypeptides corresponding to this gene are useful for the diagnosis and intervention of lung tumors. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

- 5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:80 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- 10 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1266 of SEQ ID NO:80, b is an integer of 15 to 1280, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.

15

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 71

- 20 When tested against K562 leukemia cell lines, supernatants removed from cells containing this gene activated the ISRE assay. Thus, it is likely that this gene activates leukemia cells through the Jak-STAT signal transduction pathway. The interferon-sensitive response element is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells.
- 25 Therefore, activation of the Jak-STAT pathway, reflected by the binding of the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. Furthermore, contact of cells with supernatant expressing the product of this gene increases the permeability of THP-1 monocyte cells to calcium. Thus, it is likely that the product of this gene is involved in a signal transduction pathway that is initiated
- 30 when the product of this gene binds a receptor on the surface of the monocyte cell. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating monocyte cells.

This gene is expressed primarily in adult human spleen and adult human testis.

- 35 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to

these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., spleen, testes, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:195 as residues: Pro-32 to Gly-39.

The tissue distribution in spleen, in addition to the biological activity data, indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of immune disorders. Furthermore, this gene may play a role in the survival, proliferation, and/or differentiation of hematopoietic cells in general, and may be of use in the augmentation of the numbers of stem cells and committed progenitors. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:81 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 960 of SEQ ID NO:81, b is an integer of 15 to 974, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.

30

## FEATURES OF PROTEIN ENCODED BY GENE NO: 72

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

ELSGLVIIITAWILCHSSSKNPVGGRIQLAIAIVITLFPFISWVYIYINKEMRSSWP  
THCKTVI (SEQ ID NO:611), QCPQGTETEAGVSVPPRKEGGGPYVAGLTAPHVA  
GLTAPRRVLRAMAPALWRACNGL (SEQ ID NO:612), HSSSKNPVGGRIQLA

IAIVITLFPFISWVYIY (SEQ ID NO:613), and/or RKEGGGPYVAGLTAPHVA GLTAPRRVLRAMAP (SEQ ID NO:614). Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 This gene is expressed primarily in liver tissues, and to a lesser extent in t-cell lymphoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatitis, sclerosis of the liver and cancer of the liver. Similarly,  
10 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily  
15 fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in liver indicates polynucleotides and polypeptides  
20 corresponding to this gene are useful for the diagnosis and possible treatment of diseases of the liver. Since it is primarily found in the liver, and with the additional expression seen in T-cells, it most likely deals with the immune response in the liver, for example to diseases like hepatitis, sclerosis and hepatocellular carcinoma. More generally, the tissue distribution in liver indicates polynucleotides and polypeptides  
25 corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:82 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

35 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1941 of SEQ ID NO:82, b is an integer of 15

to 1955, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:82, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 73

The gene encoding the disclosed cDNA is thought to reside on chromosome 10. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 10.

10 This gene is expressed primarily in myeloid progenitor cells, and to a lesser extent in leukemic cells and eosinophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, leukemia and other blood diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoiesis and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 The tissue distribution in immune tissues indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of leukemia. Furthermore, the polypeptides or polynucleotides are also useful to enhance or protect proliferation, differentiation, and functional activation of hematopoietic progenitor cells (e.g., bone marrow cells), useful in treating cancer patients undergoing chemotherapy or patients undergoing bone marrow transplantation. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:83 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 624 of SEQ ID NO:83, b is an integer of 15 to 638, where both a and b correspond to the positions of nucleotide residues shown in  
5 SEQ ID NO:83, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 74

10 The translation product of this gene shares sequence homology with "neurogenic secreted signaling protein (brn)" (see gill 150971) from Drosophila melanogaster which is thought to be important in the normal development of brain tissue. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: PGRPTRPAXAGLSSGGAAQEAPQADPRPWLAR (SEQ ID  
15 NO:615). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in the placenta and early embryonic tissue. Northern data has demonstrated that this gene is expressed in brain, stomach and colorectal adenocarcinoma.

20 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, several types of disorders of the brain including epilepsy, mood disorders, any of a variety of types of mental retardation, and addictive disorders  
25 including alcoholism. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain,  
30 stomach, colon, placental, embryonic, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

35 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:198 as residues: Gln-37 to Ala-42, Thr-51 to Ala-57, Pro-71 to His-79, Glu-124 to Arg-137, Ser-151 to Val-159.

The tissue distribution and homology to *Drosophila melanogaster* putative neurogenic secreted signaling protein (brn) indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment of various brain disorders as well as pre-natal testing for neuropathological conditions, such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Furthermore, the tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:84 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 845 of SEQ ID NO:84, b is an integer of 15 to 859, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:84, and where b is greater than or equal to a + 14.



**FEATURES OF PROTEIN ENCODED BY GENE NO: 75**

5 The translation product of this gene shares sequence homology with a fat-specific secreted protein.

This gene is expressed primarily in the epididymus.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic disorders and male infertility. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., epididymus, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:199 as residues: Tyr-21 to Asp-40, Ser-58 to Arg-64, Thr-71 to Ser-76, Ser-106 to Thr-112.

Homology to a fat-specific gene indicates that this gene may also play a role in the treatment and/or detection of metabolic disorders such as obesity, diabetes, anorexia nervosa and bulimia. In addition, its expression primarily in the epididymus indicates a role in the treatment/detection of male fertility disorders such as infertility, low sperm count, spermatorrhea and spermiation. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:85 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

35 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1115 of SEQ ID NO:85, b is an integer of 15

to 1129, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:85, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 76

The translation product of this gene shares sequence homology with Slit, a secreted Drosophila protein which plays a role in the development of axon pathway development in the central nervous system. The Slit protein is necessary for the normal  
10 development of the midline of the CNS, particularly the midline glial cells, and for the concomitant formation of the commissural axon pathways. The process is dependent on the level of SLIT protein expression. It appears that the SLIT protein is excreted by the midline glial cells, where it is synthesised and is eventually associated with the surfaces of axons that traverse them. Contact of cells with supernatant expressing the  
15 product of this gene increases the permeability of THP-1 monocyte cells to calcium. Thus, it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product of this gene binds a receptor on the surface of the monocyte cell. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating monocyte cells. Furthermore, when tested against  
20 U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in  
25 the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in infant brain, and to a lesser extent in adult cerebellum and frontal cortex.

30 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential  
35 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell

types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:200 as residues: Glu-25 to Lys-33, Glu-115 to Lys-120.

The tissue distribution primarily in brain and homology to Slit, a gene involved in axon pathway development, indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment/detection of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, spinal cord injury, brain injuries, crushed (optic) nerve, amyotrophic lateral sclerosis, diabetes caused nerve damage, strokes, epilepsy, multiple sclerosis, paraplegia retinal degeneration, Huntingtons Disease, facial nerve damage, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:86 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2660 of SEQ ID NO:86, b is an integer of 15 to 2674, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:86, and where b is greater than or equal to a + 14.

### 30 FEATURES OF PROTEIN ENCODED BY GENE NO: 77

The translation product of this gene shares sequence homology with human endothelial cell multimerin, which is a secreted protein that binds to the extracellular matrix and is thought to be involved in hemostasis. Multimerin is a factor V/Va-binding protein and may function as a carrier protein for platelet factor V (J. Biol Chem 1995 Aug 4;270(31):18246-51 ). Contact of cells with supernatant expressing the product of this gene increases the permeability of THP-1 Monocyte cells to calcium. Thus, it is

likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product of this gene binds a receptor on the surface of the monocyte cell. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating monocyte cells.

- 5           This gene is expressed primarily in a variety of hematopoietic cells including T-cells, dendritic cells and B-cells as well as cells and tissues of epithelial and endothelial origin including healing wounds and keratinocytes, as well as placenta.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
10   biological sample and for diagnosis of diseases and conditions which include, but are not limited to, acute internal injury, blood clotting disorders and other disorders of hemostasis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
15   the hemostasis, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endothelial, immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in  
20   healthy tissue or bodily fluid from an individual not having the disorder.

          Preferred epitopes include those comprising a sequence shown in SEQ ID NO:201 as residues: Ala-43 to Trp-57, Ser-81 to Gly-88, Tyr-125 to Asp-134, Pro-141 to Gly-154, Val-172 to Glu-178, Lys-296 to Gly-305, Leu-307 to Arg-314, Thr-335 to His-341.

- 25           The tissue distribution in endothelial tissues, and the homology to human endothelial cell multimerin, indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders involving the vasculature. Elevated expression of this gene product by endothelial cells indicates that it may play vital roles in the regulation of endothelial cell function; secretion;  
30   proliferation; or angiogenesis. Furthermore, the tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by  
35   the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene

product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells, as supported by the biological activity data mentioned previously. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:87 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1622 of SEQ ID NO:87, b is an integer of 15 to 1636, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:87, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 78

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

HYXSTPGRVPVRQFAAASTSGGPWVPGGXLEAPFQVAPSLSHSTPVFPGLI  
(SEQ ID NO:616). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in osteoblasts.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, degenerative conditions of the bone including arthritis and osteoporosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal, cancerous and wounded

tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 5 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:202 as residues: Thr-45 to Cys-50, Met-55 to Pro-60.

The tissue distribution in osteoblasts indicates polynucleotides and polypeptides corresponding to this gene are useful for treating degenerative conditions of the bone mediated by alterations in the activity ratio of osteoblasts and osteoclasts. Furthermore, elevated levels of expression of this gene product in osteoblastoma indicates that it may play a role in the survival, proliferation, and/or growth of osteoblasts. Therefore, it may be useful in influencing bone mass in such conditions as osteoporosis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 15 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:88 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- 20 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1625 of SEQ ID NO:88, b is an integer of 15 to 1639, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:88, and where b is greater than or equal to a + 14.

25

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 79

- The gene encoding the disclosed cDNA is thought to reside on chromosome 17.
- 30 Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ARGKYESAQPGGTQPEPGLGAR (SEQ ID NO:617). Polynucleotides encoding these polypeptides are also encompassed by the invention.
- 35 This gene is expressed primarily in pituitary, cerebellum and kidney and to a lesser extent in a range of fetal tissues including lung, heart and spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic, neurological, and renal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine, renal and nervous systems expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., kidney, fetal, brain, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:203 as residues: Pro-29 to Gly-34, Gln-79 to Arg-84, Arg-146 to Arg-152, Ser-183 to Ser-193, Gly-233 to His-241, Tyr-265 to Pro-278, Thr-304 to Arg-320, Leu-328 to Gly-333, Glu-385 to Arg-399.

The high expression of a secreted gene in the pituitary indicates a role for this gene or gene product in the treatment/detection of metabolic disorders associated with the endocrine system, such as growth and developmental defects. Expression in the cerebellum indicates a role in the treatment/detection of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Expression in the kidney indicates a role in the treatment/detection of renal disorders such as kidney failure, Wilms Tumor and kidney stones, as well as nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:89 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more

polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1846 of SEQ ID NO:89, b is an integer of 15 to 1860, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 80

10 The translation product of this gene shares sequence homology with ras-related proteins in rats which is thought to be involved in cellular signaling.

This gene is expressed primarily in T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune system disorders. Similarly, polypeptides and antibodies  
15 directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell  
20 types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

25 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:204 as residues: Met-40 to Thr-46, Ala-57 to Glu-64, Ser-85 to Leu-91.

The tissue distribution in immune system tissues indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. This gene product may be involved in the  
30 regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used  
35 as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility



in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may  
5 show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:90 and may have been publicly available prior to conception of the present  
10 invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 825 of SEQ ID NO:90, b is an integer of 15 to  
15 839, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14.

#### 20 FEATURES OF PROTEIN ENCODED BY GENE NO: 81

When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which  
25 are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

30 This gene is expressed primarily in fetal liver, osteoclastoma and neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the bone, haemopoietic system and cancer. Similarly,  
35 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune,

haemopoietic and bone, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, skeletal, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having  
5 such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal liver, osteoclastoma and neutrophils indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of diseases of the bone, haemopoietic and immune systems, as well as  
10 cancer. Furthermore, elevated levels of expression of this gene product in osteoclastoma indicates that it may play a role in the survival, proliferation, and/or growth of osteoclasts. Therefore, it may be useful in influencing bone mass in such conditions as osteoporosis. More generally, as evidenced by expression in fetal liver/spleen, as well as the biological activity data, this gene may play a role in the  
15 survival, proliferation, and/or differentiation of hematopoietic cells in general, and may be of use in the augmentation of the numbers of stem cells and committed progenitors. Expression of this gene product in neutrophils also indicates that it may play a role in mediating responses to infection and controlling immunological responses, such as those that occur during immune surveillance. Protein, as well as, antibodies directed  
20 against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:91 and may have been publicly available prior to conception of the present  
25 invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1131 of SEQ ID NO:91, b is an integer of 15  
30 to 1145, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:91, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 82

35

This gene is expressed primarily in endometrial stromal cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, female infertility. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:206 as residues: Gln-26 to Asn-51.

The tissue distribution in endometrial cells indicates polynucleotides and polypeptides corresponding to this gene are useful for treating female infertility. The protein product is likely involved in preparation of the endometrium of implantation and could be administered either topically or orally. Alternatively, this gene could be transfected in gene-replacement treatments into the cells of the endometrium and the protein products could be produced. Similarly, these treatments could be performed during artificial insemination for the purpose of increasing the likelihood of implantation and development of a healthy embryo. In both cases this gene or its gene product could be administered at later stages of pregnancy to promote healthy development of the endometrium. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:92 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of  $a-b$ , where  $a$  is any integer between 1 to 2036 of SEQ ID NO:92,  $b$  is an integer of 15 to 2050, where both  $a$  and  $b$  correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where  $b$  is greater than or equal to  $a + 14$ .

**FEATURES OF PROTEIN ENCODED BY GENE NO: 83.**

5           The gene encoding the disclosed cDNA is thought to reside on chromosome 19. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 19.

          This gene is expressed primarily in tissues of the central nervous system (predominantly the cerebellum) and immune system (predominantly the tonsils).

10           Nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the immune system and CNS. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the  
15   tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and neurological system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, neurological, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell  
20   sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

          Preferred epitopes include those comprising a sequence shown in SEQ ID NO:207 as residues: Pro-43 to Leu-49, Pro-61 to Gly-66, Ser-71 to Ser-83.

25           The tissue distribution in the immune system indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This  
30   gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed  
35   tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In

addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Furthermore, the tissue distribution in the central nervous system indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:93 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1159 of SEQ ID NO:93, b is an integer of 15 to 1173, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 84

This gene is expressed primarily in testes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive disorders and testes diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the testes, expression of this gene at

significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., testes, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:208 as residues: Lys-28 to His-35, Asn-58 to Gly-64, Thr-80 to Asn-86, Pro-96 to Glu-111, Pro-124 to Phe-133.

The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of testes disorders. Furthermore, the tissue distribution in testes indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:94 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 808 of SEQ ID NO:94, b is an integer of 15 to 822, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 85**

5 This gene is expressed primarily in infant brain, bone marrow and activated T-cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental, immune and hematopoietic disorders. Similarly, 10 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, hematopoietic and developmental systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, 15 developmental, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:209 as residues: Asn-23 to Val-37.

Expression in infant brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of mental retardation and other developmental disorders in addition to neurodegenerative disease states and 25 behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Expression of the gene in bone marrow and in B-cells indicates a role in the treatment and/or detection of immune disorders such as arthritis, asthma, immunodeficiency diseases and leukemia. Protein, as well as, antibodies directed 30 against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:95 and may have been publicly available prior to conception of the present 35 invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more

polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1063 of SEQ ID NO:95, b is an integer of 15 to 1077, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to a + 14.

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## FEATURES OF PROTEIN ENCODED BY GENE NO: 86

The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: SCGSSRRSAKRS�TLKLIDFSHRI (SEQ ID NO:618). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in infant brain, fetal liver and fetal spleen, and to a lesser extent in macrophages, T-cells, erythroid cells and myeloid progenitor cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, developmental and immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous, immune and developmental systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, neurological, developing, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:210 as residues: Val-34 to Leu-48, Val-51 to Gly-67, Lys-74 to Asp-81, Thr-93 to Glu-98, Ser-138 to His-149, Ala-186 to Gln-201, Pro-257 to Arg-271.

Expression in infant brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of mental retardation and other developmental disorders in addition to neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons



Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Its distribution in fetal liver and fetal spleen indicates that this gene may play a role in the development of the hematopoietic and immune systems and that it may play a role in the treatment/detection of immune system disorders such as leukemia, arthritis and asthma. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:96 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2078 of SEQ ID NO:96, b is an integer of 15 to 2092, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:96, and where b is greater than or equal to a + 14.

## 20 FEATURES OF PROTEIN ENCODED BY GENE NO: 87

This gene is expressed primarily in hippocampus, and to a lesser extent in fetal heart.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, any of a variety of brain disorders including epilepsy, stroke, palsy, and mood disorders including unipolar and bipolar depression. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain, heart, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in hippocampus indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, epilepsy, stroke, palsy, and mood disorders including unipolar and bipolar depression, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:97 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1338 of SEQ ID NO:97, b is an integer of 15 to 1352, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to a + 14.

## 25 FEATURES OF PROTEIN ENCODED BY GENE NO: 88

The translation product of this gene shares sequence homology with a C. elegans protein (coded for by C. elegans cDNA yk112f3.5). The gene encoding the disclosed cDNA is thought to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

HYFLRTVSGLSVVPVSLRCCMCPPTGPAPATAHSPFDPPALPIQFEYQQA  
(SEQ ID NO:619), QLEAEIENLSWKVERADSYDRGDLENQMHI AEQRRRT  
35 LLKDFHDT (SEQ ID NO:620), VPVSLRCCMCPPTGPAPATAHS (SEQ ID  
NO:621), and/or SWKVERADSYDRGDLENQMHI AEQR (SEQ ID NO:622).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal liver and spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, congenital disorders of the liver and spleen. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hepatic, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal liver and spleen indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). More generally, as evidenced by expression in fetal liver/spleen, this gene may play a role in the survival, proliferation, and/or differentiation of hematopoietic cells in general, and may be of use in augmentation of the numbers of stem cells and committed progenitors. Expression of this gene product in primary dendritic cells also indicates that it may play a role in mediating responses to infection and controlling immunological responses, such as those that occur during immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:98 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 899 of SEQ ID NO:98, b is an integer of 15 to 913, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 89**

5           This gene is expressed primarily in neutrophils.

          Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, acute immunological disorders such as inflammation. Similarly,  
10   polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily  
15   fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

          The tissue distribution in neutrophils indicates polynucleotides and polypeptides  
20   corresponding to this gene are useful for treating an acute inflammatory response. Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies  
25   directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion  
30   of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in neutrophils also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed  
35   tissues.

          Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ

ID NO:99 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

- Accordingly, preferably excluded from the present invention are one or more  
5 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 707 of SEQ ID NO:99, b is an integer of 15 to 721, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to a + 14.

10

### FEATURES OF PROTEIN ENCODED BY GENE NO: 90

- When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates  
15 myeloid cells through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS  
20 element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in fetal liver and fetal spleen.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
25 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental and/or immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and developmental systems,  
30 expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., liver, spleen, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily  
35 fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:214 as residues: His-23 to Leu-31, His-33 to Pro-41.

The distribution of this gene in fetal liver and fetal spleen and the biological activity data indicates it may play a role in the development of the immune and hematopoietic systems. It may, therefore, play a role in the treatment and/or detection of immune and/or hematopoietic disorders including leukemia, arthritis and asthma.

- 5 Furthermore, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for
- 10 immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the
- 15 differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ
- 20 ID NO:100 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of
- 25 a-b, where a is any integer between 1 to 631 of SEQ ID NO:100, b is an integer of 15 to 645, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:100, and where b is greater than or equal to a + 14.

### 30 FEATURES OF PROTEIN ENCODED BY GENE NO: 91

This gene is expressed primarily in brain and osteoclastoma to a lesser extent in placenta.

- Therefore, polynucleotides and polypeptides of the invention are useful as
- 35 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological, bone and reproductive disorders. Similarly, polypeptides

and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous, bone and reproductive systems, expression of this gene at significantly higher or lower levels

- 5 may be routinely detected in certain tissues or cell types (e.g., skeletal, brain, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 10 Preferred epitopes include those comprising a sequence shown in SEQ ID NO:215 as residues: Phe-47 to Cys-54.

- Expression of this gene in brain indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons
- 15 Disease, Huntingtons Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Furthermore, expression in osteoclastoma indicates a role in the treatment and/or detection of bone damage such as fractures and dislocations. Elevated levels of expression of this gene product in osteoclastoma indicates that it may play a role in the survival, proliferation, and/or growth of
- 20 osteoclasts. Therefore, it may be useful in influencing bone mass in such conditions as osteoporosis. Expression in the placenta indicates a role in the treatment and/or detection of pregnancy disorders such as miscarriage, birth defects, premature birth, in addition to disorders such as placenta previa and placentitis. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced
- 25 by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In
- 30 such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Protein, as well as, antibodies directed against the
- 35 protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:101 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 549 of SEQ ID NO:101, b is an integer of 15 to 563, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:101, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 92

This gene is expressed primarily in T-cells, bone marrow, fetal liver/spleen and and to a lesser extent in adipocytes, kidney, melanocytes and stimulated fibroblasts.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic disease characterized by alterations in T cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in immune tissues indicates polynucleotides and polypeptides corresponding to this gene are useful for treating autoimmune diseases or proliferative disorders of the developing immune system. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. This is particularly supported by the expression of this gene product in fetal liver and bone marrow, the two primary sites of definitive hematopoiesis. Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and



immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:102 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of  $a-b$ , where  $a$  is any integer between 1 to 1310 of SEQ ID NO:102,  $b$  is an integer of 15 to 1324, where both  $a$  and  $b$  correspond to the positions of nucleotide residues shown in SEQ ID NO:102, and where  $b$  is greater than or equal to  $a + 14$ .

15

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 93

The gene encoding the disclosed cDNA is thought to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4.

This gene is expressed primarily in fetal tissues including fetal liver/spleen and to a lesser extent in lung, bone marrow, adrenal gland tumor and in the Ntera2 cell line.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the adrenal gland or lungs, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developing tissues, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in fetal and developing tissues indicates polynucleotides and polypeptides corresponding to this gene are useful for treating tumors formed by

poorly differentiated cells, as well as tumors of other tissues where expression has been observed. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
5 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:103 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more  
10 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1717 of SEQ ID NO:103, b is an integer of 15 to 1731, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:103, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 94**

This gene is expressed primarily in the prostate derived cell line PC3 and fetal liver/spleen.

20 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostatic hypertrophy or prostate cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes  
25 for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the glandular tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., prostate, immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell  
30 sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:218 as residues: Leu-26 to Ser-33.

35 The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for treating diseases of the prostate including prostatic tumors or benign prostatic hypertrophy. Protein, as well as, antibodies

directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:104 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1452 of SEQ ID NO:104, b is an integer of 15 to 1466, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:104, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 95

This gene is expressed primarily in small intestine, and to a lesser extent in breast tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the small intestine. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the small intestine, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., small intestine, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:219 as residues: Glu-37 to Gly-45.

The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of diseases involving the small intestine, such as cancer of the small intestine or other tissues where expression has been indicated. Protein, as well as, antibodies directed against the

protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:105 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1289 of SEQ ID NO:105, b is an integer of 15 to 1303, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:105, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 96

This gene is expressed primarily in fast-growing tissues such as tumor and fetal tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, growth disorders such as tumorigenesis and growth retardation. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fast-growing tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., rapidly proliferating cells, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:220 as residues: Phe-32 to Cys-37.

The tissue distribution in rapidly-proliferating tissues and cells indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of growth disorders. Furthermore, the tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are

useful for the diagnosis and treatment of cancer and other proliferative disorders.

Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division.

Similarly, embryonic development also involves decisions involving cell differentiation

- 5 and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 10 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:106 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more
- 15 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1502 of SEQ ID NO:106, b is an integer of 15 to 1516, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:106, and where b is greater than or equal to a + 14.

20

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 97**

- When tested against Jurkat T-cells and U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that
- 25 this gene activates both T-cells and myeloid cells through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by
- 30 the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in placenta, and to a lesser extent in the endometrium.

- Therefore, polynucleotides and polypeptides of the invention are useful as
- 35 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pregnancy disorders. Similarly, polypeptides and antibodies directed to

these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the female reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., placental, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 10           Expression of this gene in the placenta and endometrium indicates a role in the treatment and/or detection of pregnancy disorders such as miscarriage, birth defects, premature birth, in addition to disorders such as endometriosis, placenta previa and placentitis. Furthermore, the tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of
- 15 disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a
- 20 vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation,
- 25 survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Alternatively, the tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for treating female infertility. The protein product is likely involved in preparation of the endometrium of implantation and could be administered either topically or orally. Alternatively, this gene could be
- 30 transfected in gene-replacement treatments into the cells of the endometrium and the protein products could be produced. Similarly, these treatments could be performed during artificial insemination for the purpose of increasing the likelihood of implantation and development of a healthy embryo. In both cases this gene or its gene product could be administered at later stages of pregnancy to promote healthy
- 35 development of the endometrium. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:107 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1675 of SEQ ID NO:107, b is an integer of 15 to 1689, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:107, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 98

The gene encoding the disclosed cDNA is thought to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5. Recently another group gened and sequenced this gene, calling it MDC-3.13 isoform 1 (Genbank Accession Number: g3860095), which is believed to be a cellular factor involved in the differentiation of dendritic cells. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

HEAWLRSAGTREPPREQRTRRRQTAQLALQVPAPSRTPPMATDVFNSKNLAVX  
 AQKKILGKMVSKSIATTLIDDTSSSEVLDEL YRV TREY TQNKKEAEKIIKNLIKTVI  
 KLAILYRNNQFNQDELALMEKFKKKVHQLAMTVVSFHQVDYTFDRNVLSRLL  
 NECREMLHQIIQRHLTAKSHGRVNNVFDHFSDCEFLAALYNPFGNFKPHLQKL  
 CDGINKMLDEENI (SEQ ID NO:623), HEAWLRSAGTREPPREQRTRRRQTAQLA  
 LQVPAPSRTPPMATDVFNSKNLAV (SEQ ID NO:624), XAQKKILGKMVSKSIAT  
 TLIDDTSSSEVLDEL YRV TREY TQNKKEAEKII (SEQ ID NO:625), KNLIKTVIKLA  
 ILYRNNQFNQDELALMEKFKKKVHQLAMTVVSFHQVDYTF (SEQ ID NO:626),  
 DRNVLSRLLNECREMLHQIIQRHLTAKSHGRVNNVFDHFSDCEFLAALYNPF  
 (SEQ ID NO:627), and/or GNFKPHLQKLCDGINKMLDEENI (SEQ ID NO:628).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in placenta, spleen from CLL patients and various T cell libraries, and to a lesser extent in lung, bone marrow, neutrophil, osteoclastoma, and lymphoma tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the blood particularly diseases afflicting T cells and tumors of blood cells. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., placental, immune, vascular, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in immune tissues indicates polynucleotides and polypeptides corresponding to this gene are useful for treating diseases of the blood including leukemias, lymphomas and diseases that alter T-cell function or proliferation. Furthermore, the tissue distribution in placenta indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:108 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more



polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1929 of SEQ ID NO:108, b is an integer of 15 to 1943, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:108, and where b is greater than or equal to a + 14.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 99

This gene is expressed primarily in rejected kidney, placenta, and melanocytes.

10 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, acute or chronic renal failure. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for  
15 differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the renal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., renal, placental, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample  
20 taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:223 as residues: Thr-41 to Pro-47.

25 The tissue distribution in kidney indicates polynucleotides and polypeptides corresponding to this gene are useful for treating diseases of the kidney, including renal failure of either an acute or chronic nature, as well as nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to  
30 Wilms Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available  
35 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:109 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the

scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1580 of SEQ ID NO:109, b is an integer of 15 to 1594, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:109, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 100

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When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

20

This gene is expressed primarily in spinal cord, and to a lesser extent in melanocytes and fetal spleen/liver.

25

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, central nervous system diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., central nervous system, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

35

The tissue distribution in spinal cord tissue indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of central nervous system disorders, such as Alzheimers Disease, Parkinsons Disease,

Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:110 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1728 of SEQ ID NO:110, b is an integer of 15 to 1742, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:110, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 101

This gene is expressed primarily in breast and dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast related disorders and inflammatory diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the breast tissue and dendritic cells, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., breast, immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in breast indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of breast related diseases and inflammatory disorders. Furthermore, the tissue distribution in breast indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and intervention of breast tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:111 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1487 of SEQ ID NO:111, b is an integer of 15 to 1501, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:111, and where b is greater than or equal to a + 14.

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#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 102**

When tested against sensory neuron cell lines, supernatants removed from cells containing this gene activated the EGR1 assay. Thus, it is likely that this gene activates neuronal cells through a signal transduction pathway. Early growth response 1 (EGR1) is a promoter associated with certain genes that induces various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. Furthermore, when tested against both Jurkat T-cells and U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates both T-cells and myeloid cells through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

This gene is expressed primarily in synovial sarcoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, synovial sarcoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the synovial sarcoma, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., synovium, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in synovial sarcoma, and the biological activity data, suggest that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of synovial sarcoma. In general, the expression of this gene product in synovium indicates a role in the detection and treatment of disorders and conditions afflicting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (ie. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:112 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 777 of SEQ ID NO:112, b is an integer of 15 to 791, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:112, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 103**

This gene is expressed primarily in human tonsils.

Therefore, polynucleotides and polypeptides of the invention are useful as  
5 reagents for differential identification of the tissue(s) or cell type(s) present in a  
biological sample and for diagnosis of diseases and conditions which include, but are  
not limited to, relating to inflammatory diseases such as tonsilitis, and immune system  
disorders. Similarly, polypeptides and antibodies directed to these polypeptides are  
useful in providing immunological probes for differential identification of the tissue(s)  
10 or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
the immune system, expression of this gene at significantly higher or lower levels may  
be routinely detected in certain tissues or cell types (e.g., immune, cancerous and  
wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal  
fluid) or another tissue or cell sample taken from an individual having such a disorder,  
15 relative to the standard gene expression level, i.e., the expression level in healthy tissue  
or bodily fluid from an individual not having the disorder.

The tissue distribution in tonsils indicates polynucleotides and polypeptides  
corresponding to this gene are useful for the diagnosis, treatment, and/or prevention of  
lymphoid tissue disorders such as tonsilitis. Furthermore, the tissue distribution  
20 indicates polynucleotides and polypeptides corresponding to this gene are useful for the  
diagnosis and treatment of a variety of immune system disorders. Expression of this  
gene product in tonsils indicates a role in the regulation of the proliferation; survival;  
differentiation; and/or activation of potentially all hematopoietic cell lineages, including  
blood stem cells. This gene product may be involved in the regulation of cytokine  
25 production, antigen presentation, or other processes that may also suggest a usefulness  
in the treatment of cancer (e.g. by boosting immune responses). Since the gene is  
expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies  
directed against the protein may show utility as a tumor marker and/or immunotherapy  
targets for the above listed tissues. Therefore it may be also used as an agent for  
30 immunological disorders including arthritis, asthma, immune deficiency diseases such  
as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and  
psoriasis. In addition, this gene product may have commercial utility in the expansion  
of stem cells and committed progenitors of various blood lineages, and in the  
differentiation and/or proliferation of various cell types. Protein, as well as, antibodies  
35 directed against the protein may show utility as a tumor marker and/or immunotherapy  
targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:113 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1623 of SEQ ID NO:113, b is an integer of 15 to 1637, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:113, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 104

This gene is expressed primarily in activated T-cells and prostate tissue. Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, T lymphocytes related diseases and inflammation of the prostate. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:228 as residues: Arg-24 to Trp-36. The tissue distribution in immune system tissues and prostate tissue indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune and reproductive disorders. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin,

the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in T cells also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:114 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1574 of SEQ ID NO:114, b is an integer of 15 to 1588, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:114, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 105

This gene is expressed primarily in human adult pulmonary tissue and infant brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, relating to the lung, neurological and immunological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the respiratory, nervous, and immune systems expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., pulmonary, immune, nervous, cancerous and wounded tissues) or bodily fluids (e.g.,



serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 5           The tissue distribution in pulmonary tissue and infant brain tissue indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment for disorders relating to the pulmonary system, the central nervous system, and the immune system. Furthermore, the tissue distribution in pulmonary tissue and fetal tissue indicates polynucleotides and polypeptides
- 10           corresponding to this gene are useful for the detection and treatment of disorders associated with developing lungs, particularly in premature infants where the lungs are the last tissues to develop. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and intervention of lung tumors, since the gene may be involved in the regulation of cell division.
- 15           Additionally, the tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS,
- 20           psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Also, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other
- 25           processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma,
- 30           immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a
- 35           tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ

ID NO:115 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

- Accordingly, preferably excluded from the present invention are one or more
- 5 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1912 of SEQ ID NO:115, b is an integer of 15 to 1926, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:115, and where b is greater than or equal to a + 14.

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#### FEATURES OF PROTEIN ENCODED BY GENE NO: 106

- The translation product of this gene shares sequence homology with the KIAA0132 gene product, and also shares homology to Drosophila melanogaster ring
- 15 canel protein. The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in infant brain and B-cell lymphoma.

- Therefore, polynucleotides and polypeptides of the invention are useful as
- 20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, relating to the central nervous system and B cell disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a
- 25 number of disorders of the above tissues or cells, particularly of the central nervous and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., central nervous system, immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having
- 30 such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:230 as residues: Thr-31 to Trp-42, Gly-49 to His-54, Gly-68 to Glu-75, Ser-77 to Trp-89, Met-142 to Gly-148.

- 35 The tissue distribution in infant brain and B-cell lymphomas indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention for central nervous system and immune

disorders. Furthermore, the tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Additionally, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:116 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1049 of SEQ ID NO:116, b is an integer of 15 to 1063, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:116, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 107**

When tested against sensory neuron cell lines, supernatants removed from cells containing this gene activated the EGR1 assay. Thus, it is likely that this gene activates neuronal cells through a signal transduction pathway. Early growth response 1 (EGR1) is a promoter associated with certain genes that induces various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in human gall bladder.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, relating to gastrointestinal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the gastrointestinal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., gall bladder, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:231 as residues: Pro-45 to Pro-51.

The tissue distribution in gall bladder indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of gastrointestinal disorders. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:117 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of

a-b, where a is any integer between 1 to 1601 of SEQ ID NO:117, b is an integer of 15 to 1615, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:117, and where b is greater than or equal to a + 14.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 108

This gene is expressed primarily in human whole brain.

Therefore, polynucleotides and polypeptides of the invention are useful as  
10 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of  
15 the above tissues or cells, particularly of the central nervous and endocrine systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard  
20 gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:232 as residues: Gln-58 to Asp-64, His-69 to Pro-76, Leu-101 to Glu-108.

The tissue distribution in brain tissue indicates polynucleotides and polypeptides  
25 corresponding to this gene are useful for the diagnosis and treatment of the central nervous system and endocrine system disorders. Furthermore, the tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome,  
30 schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked  
35 disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:118 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1207 of SEQ ID NO:118, b is an integer of 15 to 1221, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:118, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 109

The translation product of this gene shares sequence homology with human translation initiation factor eIF3 p40 subunit.

This gene is expressed primarily in human adipose, human fetal spleen, and dendritic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, adipose, immune and nerve cell disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., adipose, immune, nervous, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:233 as residues: Asn-27 to Ser-33, Gln-44 to Lys-50.

The tissue distribution fetal liver/spleen and dendritic cells indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of immune and nerve cell disorders. Furthermore, the tissue distribution in adipose tissue indicates polynucleotides and polypeptides corresponding

to this gene are useful for the treatment of obesity and other metabolic and endocrine conditions or disorders. Additionally, the protein product of this gene may show utility in ameliorating conditions which occur secondary to aberrant fatty-acid metabolism (e.g. aberrant myelin sheath development), either directly or indirectly. Also, the tissue distribution indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of hematopoietic disorders. This gene product is primarily expressed in hematopoietic cells and tissues, suggesting that it plays a role in the survival, proliferation, and/or differentiation of hematopoietic lineages. This is particularly supported by the expression of this gene product in fetal liver, which is a primary site of definitive hematopoiesis. Expression of this gene product in primary dendritic cells also strongly indicates a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:119 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1135 of SEQ ID NO:119, b is an integer of 15 to 1149, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:119, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 110

The translation product of this gene shares sequence homology with Ig V-chain, which is thought to be important in immune function. When tested against Jurkat cell lines, supernatants removed from cells containing this gene activated the NF-kB transcription factor. Thus, it is likely that this gene activates Jurkat cells by activating a transcriptional factor found within these cells. Nuclear factor kB is a transcription factor activated by a wide variety of agents, leading to cell activation, differentiation, or apoptosis. Reporter constructs utilizing the NF-kB promoter element are used to screen supernatants for such activity.

This gene is expressed in human synovial sarcoma, infant brain INIB cells, macrophages (GM-CSF treated), human endometrial stromal cells-treated with estradiol, human pancreas tumor, hemangiopericytoma, human endometrial tumor, chronic lymphocytic leukemia and a human colon carcinoma (HCC) cell line.

5           Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers such as human synovial sarcoma, human pancreas tumor, hemangiopericytoma, human endometrial tumor, chronic lymphocytic leukemia and  
10           human colon carcinoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune,  
15           cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

          Preferred epitopes include those comprising a sequence shown in SEQ ID  
20           NO:234 as residues: Leu-21 to Ala-30, Ser-38 to Asp-47, Pro-87 to Asp-94, Leu-197 to Thr-204, Pro-256 to Ser-262, Thr-277 to Arg-282, Thr-293 to Trp-303.

          The tissue distribution in numerous cancerous tissues, and the homology to Ig V-chain, as well as the biological activity data, indicates polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of  
25           cancers, including human synovial sarcoma, human pancreas tumor, hemangiopericytoma, human endometrial tumor, chronic lymphocytic leukemia and human colon carcinoma, as well as other tissues where expression has been demonstrated. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30           Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:120 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

35           Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1501 of SEQ ID NO:120. b is an integer of 15



to 1515, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:120, and where b is greater than or equal to a + 14.

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HFCCQ50	209463 11/14/97	Uni-ZAP XR	11	1271	1	1271	47	47	125	1	20	21	352
2	HTLAI54	209463 11/14/97	Uni-ZAP XR	12	1451	1	1451	125	125	126	1	22	23	157
3	HKABT24	209463 11/14/97	pCMVSPORT 2.0	13	2317	1	1809	66	66	127	1	22	23	553
4	HLWBF94	209463 11/14/97	pCMVSPORT 3.0	14	1472	1	1472	192	192	128	1	18	19	307
5	HFKFF78	209463 11/14/97	Uni-ZAP XR	15	1016	1	961	92	92	129	1	18	19	166
6	HSYBG37	209463 11/14/97	pCMVSPORT 3.0	16	1239	1	1239	48	48	130	1	24	25	305
7	HTHCA77	209463 11/14/97	Uni-ZAP XR	17	1405	1	1405	160	160	131	1	24	25	219

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
8	HNHEZ51	209463 11/14/97	Uni-ZAP XR	18	1534	1	1534	106	106	132	1	32	33	98
9	HFIAX46	209463 11/14/97	pSport1	19	1233	1	1233	195	195	133	1	20	21	60
10	HFOXO72	209463 11/14/97	pSport1	20	1090	1	862	240	240	134	1	32	33	247
11	HODDW40	209463 11/14/97	Uni-ZAP XR	21	682	1	682	139	139	135	1	19	20	40
12	HSAWG42	209463 11/14/97	Uni-ZAP XR	22	770	1	770	31	31	136	1	27	28	74
13	HBMSK09	209463 11/14/97	Uni-ZAP XR	23	565	1	565	67	67	137	1	28	29	74
14	HDPAU16	209463 11/14/97	pCMVSPORT 3.0	24	1356	1	1356	486	486	138	1	24	25	57
15	HFEBE12	209463 11/14/97	Uni-ZAP XR	25	617	3	617	99	99	139	1	22	23	173

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
16	HFLNB64	209463 11/14/97	Uni-ZAP XR	26	648	1	648	62	62	140	1	39	40	45
16	HCESD11	209877 05/18/98	pBluescript	121	1025	1	1025	188	188	235	1	18	19	28
17	HSAWZ41	209463 11/14/97	Uni-ZAP XR	27	1388	1	1388	98	98	141	1	24	25	57
18	HNFJF07	209463 11/14/97	Uni-ZAP XR	28	616	1	616	86	86	142	1	21	22	66
19	HNGIO57	209463 11/14/97	Uni-ZAP XR	29	828	1	828	87	87	143	1	18	19	52
20	HE7TM22	209463 11/14/97	Uni-ZAP XR	30	581	1	581	70	70	144	1	22	23	65
21	HFRBR70	209463 11/14/97	Uni-ZAP XR	31	789	1	789	40	40	145	1	20	21	56
22	HTHBK35	209463 11/14/97	Uni-ZAP XR	32	884	1	884	108	108	146	1	26	27	66

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
23	HWABA81	209463 11/14/97	pCMVSPORT 3.0	33	866	1	866	57	57	147	1	21	22	48
24	HKGAA73	209463 11/14/97	pSport1	34	1694	1	1694	38	38	148	1	27	28	88
25	HKIYP40	209463 11/14/97	pBluescript	35	1215	1	1215	43	43	149	1	32	33	76
26	HKMMW74	209463 11/14/97	pBluescript	36	1794	1	1794	202	202	150	1	21	22	41
27	HLFB127	209463 11/14/97	pBluescript SK-	37	1174	1	1174	135	135	151	1	19	20	45
28	HLQCW84	209463 11/14/97	Lambda ZAP II	38	1087	1	1087	31	31	152	1	18	19	41
29	HBNAV22	209463 11/14/97	Uni-ZAP XR	39	438	1	438	13	13	153	1	40	41	43
30	HTEAM34	209463 11/14/97	Uni-ZAP XR	40	734	1	734	63	63	154	1	28	29	122

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	5' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
31	HTHDK34	209463 11/14/97	Uni-ZAP XR	41	1346	1	1346	60	60	155	1	35	36	41
32	H6BSG32	209463 11/14/97	Uni-ZAP XR	42	998	53	998	209	209	156	1	24	25	55
33	HCFAD33	209463 11/14/97	pSportI	43	658	1	658	297	297	157	1	17	18	44
34	HDTEN81	209463 11/14/97	pCMVSPORT 2.0	44	566	1	566	114	114	158	1	17	18	85
35	HFXDT43	209463 11/14/97	Lambda ZAP II	45	1277	1	1277	92	92	159	1	19	20	44
36	HNGHQ09	209463 11/14/97	Uni-ZAP XR	46	442	1	442	65	65	160	1	17	18	68
37	HHGDF16	209463 11/14/97	Lambda ZAP II	47	890	215	890	253	253	161	1	26	27	52
38	HJBCG12	209463 11/14/97	pBluescript SK-	48	737	40	737	382	382	162	1	24	25	56

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
39	HOGAW62	209463 11/14/97	pCMVSPORT 2.0	49	571	1	571	259	259	163	1	26	27	55
40	HSWBJ74	209463 11/14/97	pCMVSPORT 3.0	50	356	1	356	43	43	164	1	35	36	47
41	HGBHR26	209511 12/03/97	Uni-ZAP XR	51	913	1	913	174	174	165	1	22	23	129
42	HKDBF34	209511 12/03/97	pCMVSPORT 1	52	1356	1	1356	18	18	166	1	19	20	104
43	H6EAB28	209511 12/03/97	Uni-ZAP XR	53	1547	1	1547	116	116	167	1	21	22	76
44	HLWAO22	209511 12/03/97	pCMVSPORT 3.0	54	1338	1	1311	212	212	168	1	21	22	354
45	HAGFH53	209511 12/03/97	Uni-ZAP XR	55	2071	1	2071	96	96	169	1	36	37	89
46	HHENQ22	209511 12/03/97	pCMVSPORT 3.0	56	1899	1	1899	115	115	170	1	36	37	58

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT: SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	5' NT of Clone Seq.	5' NT of Clone Seq.	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
47	HKMLK53	209511 12/03/97	pBluescript	57	1543	1	1543	20	20	171	1	25	26	69
48	HSKGQ58	209511 12/03/97	pBluescript	58	1133	1	1133	41	41	172	1	37	38	78
49	HNFE93	209511 12/03/97	Uni-ZAP XR	59	1490	1	1480	33	33	173	1	33	34	173
50	HAIBZ39	209511 12/03/97	Uni-ZAP XR	60	1336	1	1336	48	48	174	1	17	18	63
51	HBXFP23	209511 12/03/97	ZAP Express	61	1705	178	1705	384	384	175	1	25	26	42
52	HEQBF32	209511 12/03/97	pCMVSPORT 3.0	62	1031	1	1031	97	97	176	1	25	26	113
53	HETHE81	209511 12/03/97	Uni-ZAP XR	63	1589	1	1589	182	182	177	1	23	24	155
54	HFPAC12	209511 12/03/97	Uni-ZAP XR	64	1088	1	1088	140	140	178	1	21	22	88



Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
55	HDPFF39	209511 12/03/97	pCMVSPORT 3.0	65	1256	1	1256	175	175	179	1	18	19	196
56	HFXHD88	209511 12/03/97	Lambda ZAP II	66	1602	1	1602	130	130	180	1	41	42	128
57	HFOXV65	209511 12/03/97	pSPORT1	67	938	1	938	204	204	181	1	26	27	154
58	HKADX21	209511 12/03/97	pCMVSPORT 2.0	68	1585	122	1585	414	414	182	1	18	19	106
59	HPZAB47	209511 12/03/97	pBluescript	69	1676	1	1676	34	34	183	1	18	19	47
60	HAGFE79	209511 12/03/97	Uni-ZAP XR	70	1344	1	1344	133	133	184	1	18	19	126
61	HCE1X60	209511 12/03/97	Uni-ZAP XR	71	1474	1	1474	38	38	185	1	25	26	86
62	HFXKD36	209511 12/03/97	Lambda ZAP II	72	2012	130	2012	251	251	186	1	35	36	57

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	5' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
63	HBMCU71	209511 12/03/97	pBluescript	73	1267	1	1267	77	77	187	1	21	22	68
64	HTEIV80	209511 12/03/97	Uni-ZAP XR	74	1748	1	1748	203	203	188	1	15	16	47
65	HFIAP16	209511 12/03/97	pSport1	75	1570	38	1570	44	44	189	1	30	31	50
66	HODAV86	209511 12/03/97	Uni-ZAP XR	76	524	1	524	153	153	190	1	28	29	55
67	HTEDF80	209511 12/03/97	Uni-ZAP XR	77	1306	1	1306	696	696	191	1	21	22	126
68	HTODJ69	209511 12/03/97	Uni-ZAP XR	78	1479	1	1479	123	123	192	1	23	24	69
69	HE6GR02	209511 12/03/97	Uni-ZAP XR	79	1794	1	1794	100	100	193	1	18	19	70
70	HAPNY86	209511 12/03/97	Uni-ZAP XR	80	1280	1	1280	100	100	194	1	25	26	129

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
71	HTLDR33	209511 12/03/97	Uni-ZAP XR	81	974	1	974	368	368	195	1	19	20	54
72	HACBI61	209511 12/03/97	Uni-ZAP XR	82	1955	1	1955	174	174	196	1	16	17	79
73	HMEIK34	209511 12/03/97	Lambda ZAP II	83	638	1	638	243	243	197	1	24	25	41
74	HKAAK02	209551 12/12/97	pCMVSPORT 2.0	84	859	1	859	97	97	198	1	33	34	196
75	HEPAA46	209551 12/12/97	Uni-ZAP XR	85	1129	1	1129	18	18	199	1	20	21	123
76	HFPCX09	209551 12/12/97	Uni-ZAP XR	86	2674	59	2674	249	249	200	1	26	27	549
76	HFPCX09	209551 12/12/97	Uni-ZAP XR	122	2207	1	2207	185	185	236	1	26	27	66
77	HLWAA88	209551 12/12/97	pCMVSPORT 3.0	87	1636	1	1636	51	51	201	1	22	23	488

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
77	HLWAA88	209551 12/12/97	pCMVSPORT 3.0	123	1770	1	1770	35	237	1	22	23	113
78	HOHBV89	209551 12/12/97	pCMVSPORT 2.0	88	1639	1	1639	158	202	1	28	29	85
79	HHFBY69	209552 05/07/98	Uni-ZAP XR	89	1860	2	1860	71	203	1	25	26	399
79	HCEFL57	209551 12/12/97	Uni-ZAP XR	124	1034	1	1032	68	238	1	25	26	105
80	HMEKU83	209551 12/12/97	Lambda ZAP II	90	839	1	839	35	204	1	28	29	194
81	HOSBY40	209551 12/12/97	Uni-ZAP XR	91	1145	1	1145	89	205	1	30	31	56
82	HKFBH93	209551 12/12/97	ZAP Express	92	2050	174	2050	262	206	1	18	19	72
83	HMTAD67	209551 12/12/97	pCMVSPORT 3.0	93	1173	1	1173	306	207	1	19	20	84

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
84	HTEBP77	209551 12/12/97	Uni-ZAP XR	94	822	1	822	91	91	208	1	18	19	194
85	HE9CO69	209551 12/12/97	Uni-ZAP XR	95	1077	1	1077	161	161	209	1	26	27	41
86	HCACV51	209551 12/12/97	Uni-ZAP XR	96	2092	1	2092	173	173	210	1	31	32	281
87	HHPBI45	209551 12/12/97	Uni-ZAP XR	97	1352	1	1352	123	123	211	1	20	21	47
88	HLQDH79	209551 12/12/97	Lambda ZAP II	98	913	1	913	205	205	212	1	19	20	58
89	HNGFJ67	209551 12/12/97	Uni-ZAP XR	99	721	1	721	344	344	213	1	21	22	42
90	HEIAC52	209551 12/12/97	Uni-ZAP XR	100	645	1	645	81	81	214	1	18	19	52
91	HFXXKL58	209551 12/12/97	Lambda ZAP II	101	563	1	563	120	120	215	1	17	18	67

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of 5' NT Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
92	HMVAM60	209551 12/12/97	pSport1	102	1324	1	1324	96	96	216	1	26	27	56
93	HMVBR22	209551 12/12/97	pSport1	103	1731	1	1731	104	104	217	1	20	21	55
94	HPJCW04	209551 12/12/97	Uni-ZAP XR	104	1466	1	1466	44	44	218	1	19	20	57
95	HSIDJ81	209551 12/12/97	Uni-ZAP XR	105	1303	1	1303	8	8	219	1	22	23	58
96	HSLFU05	209551 12/12/97	Uni-ZAP XR	106	1516	1	1516	166	166	220	1	30	31	44
97	HEQAK71	209551 12/12/97	pCMVSPORT 3.0	107	1689	1	1689	198	198	221	1	17	18	44
98	HOSEQ49	209551 12/12/97	Uni-ZAP XR	108	1943	280	1935	544	544	222	1	32	33	51
99	HRAAM50	209551 12/12/97	pCMVSPORT 3.0	109	1594	1	1594	29	29	223	1	14	15	72

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
100	HSDFW45	209551 12/12/97	Uni-ZAP XR	110	1742	1	1742	118	118	224	1	19	20	70
101	HSLCQ82	209551 12/12/97	Uni-ZAP XR	111	1501	1	1501	233	233	225	1	22	23	57
102	HSSFT08	209551 12/12/97	Uni-ZAP XR	112	791	1	791	125	125	226	1	34	35	58
103	HTOIW31	209551 12/12/97	Uni-ZAP XR	113	1637	1	1637	107	107	227	1	19	20	42
104	HTXKQ85	209551 12/12/97	Uni-ZAP XR	114	1588	1	1588	61	61	228	1	28	29	40
105	HUFBK08	209551 12/12/97	pSport1	115	1926	1	1926	114	114	229	1	17	18	41
106	HAAJAW31	209551 12/12/97	pCMVSPORT 3.0	116	1063	1	1063	41	41	230	1	22	23	164
107	HBJEE48	209551 12/12/97	Uni-ZAP XR	117	1615	1	1615	97	97	231	1	43	44	51

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
108	HBXGH74	209551 12/12/97	ZAP Express	118	1221	1	1221	188	188	232	1	20	21	129
109	HWBDM68	209551 12/12/97	pCMVSPORT 3.0	119	1149	1	1130	368	368	233	1	24	25	54
110	HTPBW79	209511 12/03/97	Uni-ZAP XR	120	1515	118	1507	302	302	234	1	24	25	362



Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to the secreted proteins encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are species homologs. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for the desired homologue.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below).

It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

5           The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified by the one-step method described in Smith and Johnson, *Gene* 67:31-40 (1988). Polypeptides of the invention also can be purified from natural or recombinant sources  
10       using antibodies of the invention raised against the secreted protein in methods which are well known in the art.

### Signal Sequences

Methods for predicting whether a protein has a signal sequence, as well as the  
15       cleavage point for that sequence, are available. For instance, the method of McGeoch, *Virus Res.* 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, *Nucleic Acids Res.* 14:4683-4690 (1986) uses the information  
20       from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, *supra.*) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

In the present case, the deduced amino acid sequence of the secreted polypeptide  
25       was analyzed by a computer program called SignalP (Henrik Nielsen et al., *Protein Engineering* 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results  
30       shown in Table 1.

As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., +  
35       or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely

uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

#### 10 **Polynucleotide and Polypeptide Variants**

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

15 By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown in Table 1, the ORF (open reading frame), or any fragment specified as described herein.

25 As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are:

35 Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization

Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query

amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequences shown in Table 1 or to the amino acid sequence encoded by deposited DNA clone can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., *J. Biol. Chem.* 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after

deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as to have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.



The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

### Polynucleotide and Polypeptide Fragments

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clone or shown in SEQ ID NO:X. The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in the deposited clone or the nucleotide sequence shown in SEQ ID NO:X. These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

In the present invention, a "polypeptide fragment" refers to a short amino acid sequence contained in SEQ ID NO:Y or encoded by the cDNA contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-

60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred.

5 Similarly, polynucleotide fragments encoding these polypeptide fragments are also preferred.

Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions. Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotide  
10 fragments encoding these domains are also contemplated.

Other preferred fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.  
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### Epitopes & Antibodies

In the present invention, "epitopes" refer to polypeptide fragments having antigenic or immunogenic activity in an animal, especially in a human. A preferred embodiment of the present invention relates to a polypeptide fragment comprising an epitope, as well as the polynucleotide encoding this fragment. A region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." In contrast, an "immunogenic epitope" is defined as a part of a protein that elicits an antibody response. (See, for instance, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983).)  
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30 Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

In the present invention, antigenic epitopes preferably contain a sequence of at least seven, more preferably at least nine, and most preferably between about 15 to about 30 amino acids. Antigenic epitopes are useful to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe, J. G. et al., Science 219:660-666 (1983).)  
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Similarly, immunogenic epitopes can be used to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow, M. et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle, F. J. et al., J. Gen. Virol. 66:2347-2354 (1985).) A preferred immunogenic epitope includes the secreted protein. The immunogenic epitopes may be presented together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough (at least about 25 amino acids), without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting.)

As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')<sub>2</sub> fragments) which are capable of specifically binding to protein. Fab and F(ab')<sub>2</sub> fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl et al., J. Nucl. Med. 24:316-325 (1983).) Thus, these fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library. Moreover, antibodies of the present invention include chimeric, single chain, and humanized antibodies.

### **Fusion Proteins**

Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the

polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

- Moreover, polypeptides of the present invention, including fragments, and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., *Nature* 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., *J. Biochem.* 270:3958-3964 (1995).)
- Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); K. Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995).)

- Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., *Cell* 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

### Vectors, Host Cells, and Protein Production

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant  
5 techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such  
10 as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac  
15 promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a  
20 translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin  
25 resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as E. coli, Streptomyces and Salmonella typhimurium cells; fungal cells, such as yeast cells; insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and  
30 conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech,  
35 Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods  
5 In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography,  
10 phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention, and preferably the secreted form, can also  
15 be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production  
20 procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein  
25 after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

### 30 Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

The polynucleotides of the present invention are useful for chromosome  
35 identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat

polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be  
5 selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the  
10 polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome  
15 specific-cDNA libraries.

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al.,  
20 "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides  
25 correspond to the noncoding regions of the cDNAs because the coding sequences are more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage  
30 analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease  
35 could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined.



First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using polynucleotides of the present invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Both methods rely on binding of the polynucleotide to DNA or RNA. For these techniques, preferred polynucleotides are usually 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991) ) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying

personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

- 5           The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set  
10 of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

- Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as  
15 tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more  
20 restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

- There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of  
25 unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

- 30           In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using  
35 DNA immunization techniques, and as an antigen to elicit an immune response.

### Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

5 A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell. Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene  
10 expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99mTc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

15 In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for  
20 NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, 131I,  
25 112In, 99mTc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human  
30 subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The  
35 Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder.

Moreover, polypeptides of the present invention can be used to treat disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B), to inhibit the activity of a polypeptide (e.g., an oncogene), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

### **Biological Activities**

The polynucleotides and polypeptides of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides could be used to treat the associated disease.

### **Immune Activity**

A polypeptide or polynucleotide of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the

proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders  
5 may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, a polynucleotide or polypeptide of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

A polynucleotide or polypeptide of the present invention may be useful in  
10 treating or detecting deficiencies or disorders of hematopoietic cells. A polypeptide or polynucleotide of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to:  
15 blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

Moreover, a polypeptide or polynucleotide of the present invention could also  
20 be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotide or polypeptide of the present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet  
25 disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, a polynucleotide or polypeptide of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

A polynucleotide or polypeptide of the present invention may also be useful in  
30 treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of a polypeptide or polynucleotide of the  
35 present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Alternatively, a polypeptide or polynucleotide or other cells which can inhibit the hyperproliferative disorder, for example, by increasing an immune response or inhibiting the proliferation of the hyperproliferative disorder or T-cells, hyperproliferative disorders can be treated or detected by either enhancing an existing immune response. Alternatively, a method of treating hyperproliferative disorders

Examples of hyperproliferative disorders that can be treated or detected by a polypeptide or polynucleotide of the present invention include: melanoma, leukemia, lymphoma, carcinoma of the abdomen, bone, breast, digestive system, endocrine glands (adrenal, parathyroid, pituitary), head and neck, nervous (central and peripheral), skin, soft tissue, spleen, thoracic, and urogenital. Additionally, other hyperproliferative disorders can be treated or detected by a polypeptide or polynucleotide of the present invention. Hyperproliferative disorders include, but are not limited to: leukemia, lymphoma, carcinoma, multiple myeloma, paraneoplastic syndromes, paraproteinemias, purpura, Waldenström's Macroglobulinemia, Gaucher's disease, hyperproliferative disease, besides neoplasia

### Disease

A polypeptide or polynucleotide of the present invention can be used as an immunomodulatory agent. For example, by increasing the proliferation and differentiation of B and T cells. The immune response may be increased by increasing the production of antibodies, or by initiating a new immune response. Alternatively, a polynucleotide of the present invention can be used to treat or detect an infectious agent. Examples of infectious agents are one example of an infectious agent that can be treated or detected by a polynucleotide of the present invention. Examples of viruses, include, but are not limited to: Herpesviridae, Adenoviridae, Rotaviridae, Bunyaviridae, Caliciviridae, Circoviridae, and Hepatitis viruses (Hepatitis A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, R, S, T, U, V, W, X, Y, Z, AA, AB, AC, AD, AE, AF, AG, AH, AI, AJ, AK, AL, AM, AN, AO, AP, AQ, AR, AS, AT, AU, AV, AW, AX, AY, AZ, BA, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BM, BN, BO, BP, BQ, BR, BS, BT, BU, BV, BW, BX, BY, BZ, CA, CB, CC, CD, CE, CF, CG, CH, CI, CJ, CK, CL, CM, CN, CO, CP, CQ, CR, CS, CT, CU, CV, CW, CX, CY, CZ, DA, DB, DC, DD, DE, DF, DG, DH, DI, DJ, DK, DL, DM, DN, DO, DP, DQ, DR, DS, DT, DU, DV, DW, DX, DY, DZ, EA, EB, EC, ED, EE, EF, EG, EH, EI, EJ, EK, EL, EM, EN, EO, EP, EQ, ER, ES, ET, EU, EV, EW, EX, EY, EZ, FA, FB, FC, FD, FE, FF, FG, FH, FI, FJ, FK, FL, FM, FN, FO, FP, FQ, FR, FS, FT, FU, FV, FW, FX, FY, FZ, GA, GB, GC, GD, GE, GF, GG, GH, GI, GJ, GK, GL, GM, GN, GO, GP, GQ, GR, GS, GT, GU, GV, GW, GX, GY, GZ, HA, HB, HC, HD, HE, HF, HG, HH, HI, HJ, HK, HL, HM, HN, HO, HP, HQ, HR, HS, HT, HU, HV, HW, HX, HY, HZ, IA, IB, IC, ID, IE, IF, IG, IH, II, IJ, IK, IL, IM, IN, IO, IP, IQ, IR, IS, IT, IU, IV, IW, IX, IY, IZ, JA, JB, JC, JD, JE, JF, JG, JH, JI, JJ, JK, JL, JM, JN, JO, JP, JQ, JR, JS, JT, JU, JV, JW, JX, JY, JZ, KA, KB, KC, KD, KE, KF, KG, KH, KI, KJ, KK, KL, KM, KN, KO, KP, KQ, KR, KS, KT, KU, KV, KW, KX, KY, KZ, LA, LB, LC, LD, LE, LF, LG, LH, LI, LJ, LK, LL, LM, LN, LO, LP, LQ, LR, LS, LT, LU, LV, LW, LX, LY, LZ, MA, MB, MC, MD, ME, MF, MG, MH, MI, MJ, MK, ML, MM, MN, MO, MP, MQ, MR, MS, MT, MU, MV, MW, MX, MY, MZ, NA, NB, NC, ND, NE, NF, NG, NH, NI, NJ, NK, NL, NM, NN, NO, NP, NQ, NR, NS, NT, NU, NV, NW, NX, NY, NZ, OA, OB, OC, OD, OE, OF, OG, OH, OI, OJ, OK, OL, OM, ON, OO, OP, OQ, OR, OS, OT, OU, OV, OW, OX, OY, OZ, PA, PB, PC, PD, PE, PF, PG, PH, PI, PJ, PK, PL, PM, PN, PO, PP, PQ, PR, PS, PT, PU, PV, PW, PX, PY, PZ, QA, QB, QC, QD, QE, QF, QG, QH, QI, QJ, QK, QL, QM, QN, QO, QP, QQ, QR, QS, QT, QU, QV, QW, QX, QY, QZ, RA, RB, RC, RD, RE, RF, RG, RH, RI, RJ, RK, RL, RM, RN, RO, RP, RQ, RR, RS, RT, RU, RV, RW, RX, RY, RZ, SA, SB, SC, SD, SE, SF, SG, SH, SI, SJ, SK, SL, SM, SN, SO, SP, SQ, SR, SS, ST, SU, SV, SW, SX, SY, SZ, TA, TB, TC, TD, TE, TF, TG, TH, TI, TJ, TK, TL, TM, TN, TO, TP, TQ, TR, TS, TT, TU, TV, TW, TX, TY, TZ, UA, UB, UC, UD, UE, UF, UG, UH, UI, UJ, UK, UL, UM, UN, UO, UP, UQ, UR, US, UT, UY, UZ, VA, VB, VC, VD, VE, VF, VG, VH, VI, VJ, VK, VL, VM, VN, VO, VP, VQ, VR, VS, VT, VU, VV, VW, VX, VY, VZ, WA, WB, WC, WD, WE, WF, WG, WH, WI, WJ, WK, WL, WM, WN, WO, WP, WQ, WR, WS, WT, WU, WV, WW, WX, WY, WZ, XA, XB, XC, XD, XE, XF, XG, XH, XI, XJ, XK, XL, XM, XN, XO, XP, XQ, XR, XS, XT, XU, XV, XW, XX, XY, XZ, YA, YB, YC, YD, YE, YF, YG, YH, YI, YJ, YK, YL, YM, YN, YO, YP, YQ, YR, YS, YT, YU, YV, YW, YX, YY, YZ, ZA, ZB, ZC, ZD, ZE, ZF, ZG, ZH, ZI, ZJ, ZK, ZL, ZM, ZN, ZO, ZP, ZQ, ZR, ZS, ZT, ZU, ZV, ZW, ZX, ZY, ZZ.

Examples of autoimmune disorders that can be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly severe asthma) or other respiratory problems, may also be treated by a polypeptide or polynucleotide of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

A polynucleotide or polypeptide of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of immune cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, a polypeptide or polynucleotide of the present invention may be used to modulate inflammation. For example, the polypeptide or polynucleotide may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., sepsis, shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia/reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., IL-1.)

### Hyperproliferative Disorders

A polypeptide or polynucleotide can be used to treat or detect hyperproliferative disorders, including neoplasms. A polypeptide or polynucleotide of the present invention may inhibit the proliferation of the disorder through direct or indirect

Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Pasteurellaceae Infections (e.g., Actinobacillus, Haemophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Preferably, treatment using a polypeptide or polynucleotide of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

### **Regeneration**

A polynucleotide or polypeptide of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vascular (including vascular endothelium), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, a polynucleotide or polypeptide of the present invention may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. A polynucleotide or polypeptide of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue



regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using a polynucleotide or polypeptide of the present invention to proliferate and differentiate  
5 nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized  
10 neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotide or polypeptide of the present invention.

#### 15 **Chemotaxis**

A polynucleotide or polypeptide of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of  
20 hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

A polynucleotide or polypeptide of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system  
25 disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that a polynucleotide or polypeptide of the present  
30 invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, a polynucleotide or polypeptide of the present invention could be used as an inhibitor of chemotaxis.

#### **Binding Activity**

35 A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit

(antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptide from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying  
5 agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

### **Other Activities**

10 A polypeptide or polynucleotide of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide or polynucleotide of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color,  
15 skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide or polynucleotide of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide or polynucleotide of the present invention may be used to change  
20 a mammal's mental state or physical state by influencing biorhythms, circadian rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

25 A polypeptide or polynucleotide of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

### **Other Preferred Embodiments**

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of  
30 SEQ ID NO:X wherein X is any integer as defined in Table 1.

35 Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of

positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type

Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous  
5 nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete  
10 open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising  
15 a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

20 A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone  
25 identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95%  
30 identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of  
35 comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.



Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide  
5 comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

10 Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

15 Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid  
20 sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human  
25 cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an  
30 individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of  
35 illustration and are not intended as limiting.

### Examples

#### Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

5 Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For  
10 example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

	<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited Plasmid</u>
	Lambda Zap	pBluescript (pBS)
	Uni-Zap XR	pBluescript (pBS)
15	Zap Express	pBK
	lafmid BA	plafmid BA
	pSport1	pSport1
	pCMVSPORT 2.0	pCMVSPORT 2.0
	pCMVSPORT 3.0	pCMVSPORT 3.0
20	pCR <sup>®</sup> 2.1	pCR <sup>®</sup> 2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are  
25 commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer  
30 sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.

35 Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain

DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., *Focus* 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with <sup>32</sup>P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25  $\mu$ l of reaction mixture with 0.5  $\mu$ g of the above cDNA template. A convenient reaction mixture is 1.5-5 mM  $MgCl_2$ , 0.01% (w/v) gelatin, 20  $\mu$ M each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is

used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

5

**Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide**

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

10

**Example 3: Tissue Distribution of Polypeptide**

Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P<sup>32</sup> using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

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Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70°C overnight, and the films developed according to standard procedures.

25

**Example 4: Chromosomal Mapping of the Polynucleotides**

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on

30

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either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

5 **Example 5: Bacterial Expression of a Polypeptide**

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as  
10 BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp<sup>r</sup>), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site  
15 (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses  
20 the lacI repressor and also confers kanamycin resistance (Kan<sup>r</sup>). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml).  
25 The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.<sup>600</sup>) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

30 Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from  
35 QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high

affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed  
5 with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The  
10 recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer  
15 plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a  
20 neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (*lacIq*). The origin of replication (*oriC*) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

25 DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or  
30 Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

#### 35 Example 6: Purification of a Polypeptide from an Inclusion Body



The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell  
5 culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a  
10 high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M  
15 NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

20 Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

25 To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted  
30 with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem

columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column  
5 volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant  $A_{280}$  monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above  
10 refolding and purification steps. No major contaminant bands should be observed from Commaeie blue stained 16% SDS-PAGE gel when 5  $\mu$ g of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

#### 15 Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus  
20 (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The  
25 inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as  
30 long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the  
35 AUG initiation codon and the naturally associated leader sequence identified in Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring

signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures,"

- 5 Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

- 10 The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

- 15 The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

- 20 Five  $\mu$ g of a plasmid containing the polynucleotide is co-transfected with 1.0  $\mu$ g of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One  $\mu$ g of BaculoGold™ virus DNA and 5  $\mu$ g of the plasmid are mixed in a sterile well of a  
25 microtiter plate containing 50  $\mu$ l of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10  $\mu$ l Lipofectin plus 90  $\mu$ l Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then  
30 incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

- After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life  
35 Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture

and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 µCi of <sup>35</sup>S-methionine and 5 µCi <sup>35</sup>S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

#### 20 **Example 8: Expression of a Polypeptide in Mammalian Cells**

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

5           The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and  
10 Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a  
15 chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the  
20 CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse  
25 DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol  
30 outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially  
35 available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five  $\mu$ g of the expression plasmid pC6 is cotransfected with 0.5  $\mu$ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1  $\mu$ M, 2  $\mu$ M, 5  $\mu$ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200  $\mu$ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

#### **Example 9: Protein Fusions**

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the half-life time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

5 For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that  
10 the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a  
15 heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

```

GGGATCCGGAGCCCAAATCTTCTGACAAACTCACACATGCCCACCGTGCC
CAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCAAAACC
20 CAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGT
GGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG
GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAAC
AGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG
AATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAACCCCC
25 ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGT
GTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCT
GACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGTGGAGTGGGA
GAGCAATGGGCAGCCGGAGAACAATAAGACCACGCCTCCCGTGCTGG
ACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCA
30 GGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGC
ACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGAGTGC
GACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

```

#### **Example 10: Production of an Antibody from a Polypeptide**

35 The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) For example, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera

containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

5           In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., *Nature* 256:495 (1975); Köhler et al., *Eur. J. Immunol.* 6:511 (1976); Köhler et al., *Eur. J. Immunol.* 6:292 (1976); Hammerling et al., in: *Monoclonal Antibodies and T-Cell*  
10 *Hybridomas*, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at  
15 about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

          The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line  
20 (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (*Gastroenterology* 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

25           Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a  
30 mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific  
35 antibodies.



It will be appreciated that Fab and F(ab')<sub>2</sub> and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). Alternatively, 5 secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies 10 described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 15 (1985).)

#### **Example 11: Production Of Secreted Protein For High-Throughput Screening Assays**

The following protocol produces a supernatant containing a polypeptide to be 20 tested. This supernatant can then be used in the Screening Assays described in Examples 13-20.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) 25 and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

30 Plate 293T cells (do not carry cells past P+20) at  $2 \times 10^5$  cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine 35 (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in

- Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

- Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37°C for 6 hours.

- While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl<sub>2</sub> (anhyd); 0.00130 mg/L CuSO<sub>4</sub>·5H<sub>2</sub>O; 0.050 mg/L of Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O; 0.417 mg/L of FeSO<sub>4</sub>·7H<sub>2</sub>O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl<sub>2</sub>; 48.84 mg/L of MgSO<sub>4</sub>; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO<sub>3</sub>; 62.50 mg/L of NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O; 71.02 mg/L of Na<sub>2</sub>HPO<sub>4</sub>; .4320 mg/L of ZnSO<sub>4</sub>·7H<sub>2</sub>O; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitic Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H<sub>2</sub>O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H<sub>2</sub>O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H<sub>2</sub>O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H<sub>2</sub>O; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B<sub>12</sub>; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine;

0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37°C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

#### **Example 12: Construction of GAS Reporter Construct**

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN- $\alpha$ , IFN- $\gamma$ , and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

	<u>Ligand</u>	<u>tyk2</u>	<u>JAKs</u> <u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>	<u>STATS</u>	<u>GAS(elements) or ISRE</u>
	<u>IFN family</u>						
5	IFN-a/B	+	+	-	-	1,2,3	ISRE
	IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
	Il-10	+	?	?	-	1,3	
	<u>gp130 family</u>						
10	IL-6 (Pleiotrohic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
	Il-11(Pleiotrohic)	?	+	?	?	1,3	
	OnM(Pleiotrohic)	?	+	+	?	1,3	
	LIF(Pleiotrohic)	?	+	+	?	1,3	
	CNTF(Pleiotrohic)	-/+	+	+	?	1,3	
15	G-CSF(Pleiotrohic)	?	+	?	?	1,3	
	IL-12(Pleiotrohic)	+	-	+	+	1,3	
	<u>g-C family</u>						
20	IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
	IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
	IL-7 (lymphocytes)	-	+	-	+	5	GAS
	IL-9 (lymphocytes)	-	+	-	+	5	GAS
	IL-13 (lymphocyte)	-	+	?	?	6	GAS
	IL-15	?	+	?	+	5	GAS
25	<u>gp140 family</u>						
	IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
	IL-5 (myeloid)	-	-	+	-	5	GAS
	GM-CSF (myeloid)	-	-	+	-	5	GAS
30	<u>Growth hormone family</u>						
	GH	?	-	+	-	5	
	PRL	?	+/-	+	-	1,3,5	
	EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
35	<u>Receptor Tyrosine Kinases</u>						
	EGF	?	+	+	-	1,3	GAS (IRF1)
	PDGF	?	+	+	-	1,3	
	CSF-1	?	+	+	-	1,3	GAS (not IRF1)
40							

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCTCCGAAATCTAGATTTCCTCCGAAATGATTTCCTCCG  
 10 AAATGATTTCCTCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTGGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCTCCGAAATCTAGATTTCCTCCGAAATGATTTCCTCCGAAATG  
 20 ATTTTCCTCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCC  
 CTAATCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGC  
 CCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGC  
 CTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTT  
 TGCAAAAAAGCTT:3' (SEQ ID NO:5)

25 With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase,  
 30 alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter  
 35 element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using Sall and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning  
5 site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules  
10 containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter  
15 construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

**Example 13: High-Throughput Screening Assay for T-cell Activity.**

The following protocol is used to assess T-cell activity by identifying factors,  
20 such as growth factors and cytokines, that may proliferate or differentiate T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and  
25 Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately  
30 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to  
35 generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies)

with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells ( $10^7$  per transfection), and resuspend in OPTI-MEM to a final concentration of  $10^7$  cells/ml. Then add 1ml of  $1 \times 10^7$  cells in OPTI-MEM to T25 flask and incubate at 37°C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing a polypeptide as produced by the protocol described in Example 11.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100,000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophane covers) and stored at -20°C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4°C and serve as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

#### **Example 14: High-Throughput Screening Assay Identifying Myeloid Activity**



The following protocol is used to assess myeloid activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest  $2 \times 10^7$  U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ , 1 mM  $\text{MgCl}_2$ , and 675 uM  $\text{CaCl}_2$ . Incubate at  $37^\circ\text{C}$  for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at  $37^\circ\text{C}$  for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting  $1 \times 10^8$  cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of  $5 \times 10^5$  cells/ml. Plate 200 ul cells per well in the 96-well plate (or  $1 \times 10^5$  cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at  $37^\circ\text{C}$  for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.

#### **Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.**

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon

activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or  
5 differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

10 The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

15 Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

20 To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker)  
25 containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

30 Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

35 To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS

(Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count  
5 the cell number and add more low serum medium to reach final cell density as  $5 \times 10^5$  cells/ml.

Add 200  $\mu$ l of the cell suspension to each well of 96-well plate (equivalent to  $1 \times 10^5$  cells/well). Add 50  $\mu$ l supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR  
10 can be used, such as 50 ng/ $\mu$ l of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

#### **Example 16: High-Throughput Screening Assay for T-cell Activity**

15 NF- $\kappa$ B (Nuclear Factor  $\kappa$ B) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF- $\kappa$ B regulates  
the expression of genes involved in immune cell activation, control of apoptosis (NF-  
20  $\kappa$ B appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF-  $\kappa$ B is retained in the cytoplasm with I- $\kappa$ B (Inhibitor  $\kappa$ B). However, upon stimulation, I-  $\kappa$ B is phosphorylated and degraded, causing NF-  $\kappa$ B to shuttle to the nucleus, thereby activating transcription of target  
25 genes. Target genes activated by NF-  $\kappa$ B include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF- $\kappa$ B promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF- $\kappa$ B would be useful in treating  
30 diseases. For example, inhibitors of NF- $\kappa$ B could be used to treat those diseases related to the acute or chronic activation of NF- $\kappa$ B, such as rheumatoid arthritis.

To construct a vector containing the NF- $\kappa$ B promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF- $\kappa$ B binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5 5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGGAC  
TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

10 PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

15 5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGGACTTTCC  
ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCCA  
TCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACT  
AATTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGCCTCTGAGCTATTC  
20 CAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:  
3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2- promoter plasmid (Clontech) with this NF- $\kappa$ B/SV40 fragment using XhoI and HindIII.

25 However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF- $\kappa$ B/SV40/SEAP cassette is removed from the above NF- $\kappa$ B/SEAP vector using restriction enzymes Sall and NotI, and inserted into a vector containing neomycin resistance. Particularly, the

30 NF- $\kappa$ B/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with Sall and NotI.

Once NF- $\kappa$ B/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described

in Example 13. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

#### **Example 17: Assay for SEAP Activity**

5 As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

10 Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 µl of 2.5x dilution buffer into Optiplates containing 35 µl of a supernatant. Seal the plates with a plastic sealer and incubate at 65°C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 µl Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 µl Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

20 Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

#### **Reaction Buffer Formulation:**

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25

28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

**Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability**

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-3, used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO<sub>2</sub> incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-3 is made in 10% pluronic acid DMSO. To load the cells with fluo-3, 50 ul of 12 ug/ml fluo-3 is added to each well. The plate is

incubated at 37°C in a CO<sub>2</sub> incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10<sup>6</sup> cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-3 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37°C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10<sup>6</sup> cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-3. The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular Ca<sup>++</sup> concentration.

#### **Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity**

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating

tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately  
5 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from  
Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with  
100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr  
with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine  
(50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or  
10 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed  
with PBS and stored at 4°C. Cell growth on these plates is assayed by seeding 5,000  
cells/well in growth medium and indirect quantitation of cell number through use of  
AlamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento,  
CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are  
15 used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture  
plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of  
Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium.  
Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20  
20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example  
11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH  
7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub>  
and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim  
(Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for  
25 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract  
filtered through the 0.45 mm membrane bottoms of each well using house vacuum.  
Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum  
manifold and immediately placed on ice. To obtain extracts clarified by centrifugation,  
the content of each well, after detergent solubilization for 5 minutes, is removed and  
30 centrifuged for 15 minutes at 4°C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many  
methods of detecting tyrosine kinase activity are known, one method is described here.

Generally, the tyrosine kinase activity of a supernatant is evaluated by  
determining its ability to phosphorylate a tyrosine residue on a specific substrate (a  
35 biotinylated peptide). Biotinylated peptides that can be used for this purpose include  
PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and



PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg<sub>2+</sub> (5mM ATP/50mM MgCl<sub>2</sub>), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30°C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

10 The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37°C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37°C for one hour. Wash the well as above.

20 Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

#### 25 **Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity**

As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

30  
35

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4°C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

#### **Example 21: Method of Determining Alterations in a Gene** **Corresponding to a Polynucleotide**

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky, D., et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR

products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton, T.A. and Graham, M.W., *Nucleic Acids Research*, 19:1156 (1991) and sequenced with T7  
5 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-  
10 triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson, Cg. et al., *Methods Cell Biol.* 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and  
15 propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson, Cv. et al., *Genet. Anal. Tech. Appl.*, 8:75 (1991).) Image collection, analysis and  
20 chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

25

**Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample**

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is  
30 a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with  
35 specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10.

The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

#### **Example 23: Formulating a Polypeptide**

The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1 µg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1 µg/kg/hour to about 50 µg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracisternally, intravaginally,

intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes  
5 of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules.  
10 Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and R. Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric  
15 acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008;  
20 U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is  
25 formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are  
30 known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood  
35 of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

35

**Example 24: Method of Treating Decreased Levels of the Polypeptide**

It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

#### **Example 25: Method of Treating Increased Levels of the Polypeptide**

Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

#### **Example 26: Method of Treatment Using Gene Therapy**

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

5       The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the  
10       presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

      The amphotropic pA317 or GP+am12 packaging cells are grown in tissue  
15       culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

20       Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media  
25       from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

30       The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

      It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and,  
35       therefore, are within the scope of the appended claims.

      The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other



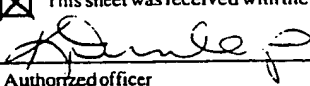
disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties.

5

Applicant's or agent's file reference number	PZ021PCT	International application No.	unassigned
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

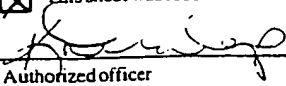
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Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 14 November 1997	Accession Number 209463
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	
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Form PCT/RO/134 (July 1992)

Applicant's or agent's file reference number	PZ021PCT	International application No	unassigned
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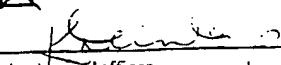
(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>174</u> . line <u>N/A</u>	
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Date of deposit 18 May 1998	Accession Number 209877
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Applicant's or agent's file reference number	PZ021PCT	International application No	unassigned
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(PCT Rule 13bis)

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Applicant's or agent's file reference number	PZ021PCT	International application No.	unassigned
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(PCT Rule 13bis)

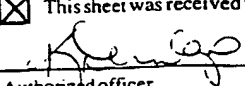
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Form PCT/RO/134 (July 1992)

Applicant's or agent's file reference number	PZ021PCT	International application No	unassigned
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(PCT Rule 13bis)

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Date of deposit 7 May 1998	Accession Number 209852
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
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Form PCT/RO/134 (July 1992)

*What Is Claimed Is:*

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X, having biological activity;

(f) a polynucleotide which is a variant of SEQ ID NO:X;

(g) a polynucleotide which is an allelic variant of SEQ ID NO:X;

(h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;

(i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.
5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.
6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.
7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.
8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.
9. A recombinant host cell produced by the method of claim 8.
10. The recombinant host cell of claim 9 comprising vector sequences.
11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:
  - (a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
  - (b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;
  - (c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
  - (d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
  - (e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
  - (f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;



- (g) a variant of SEQ ID NO:Y;
- (h) an allelic variant of SEQ ID NO:Y; or
- (i) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:  
(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and  
(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

- (a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and
- (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

- (a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and
- (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

- (a) contacting the polypeptide of claim 11 with a binding partner; and
- (b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay, wherein the method comprises:

- (a) expressing SEQ ID NO:X in a cell;
- (b) isolating the supernatant;
- (c) detecting an activity in a biological assay; and
- (d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

<110> Human Genome Sciences, Inc. et al

<120> 110 Human Secreted Proteins

<130> PZ021PCT

<140> PCT/US98/27059

<141> 1998-12-17

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**SUBSTITUTE SHEET (RULE 26)**

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&lt;211&gt; 2317

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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&lt;223&gt; n equals a,t,g, or c

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&lt;223&gt; n equals a,t,g, or c

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&lt;211&gt; 1472

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 14

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&lt;210&gt; 15

&lt;211&gt; 1016

&lt;212&gt; DNA



&lt;213&gt; Homo sapiens

&lt;400&gt; 15

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&lt;211&gt; 1239

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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&lt;211&gt; 1405

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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&lt;210&gt; 19

&lt;211&gt; 1233

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (491)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (493)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (497)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 19

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&lt;210&gt; 20

&lt;211&gt; 1090

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (4)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (17)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (47)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1033)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 20

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&lt;210&gt; 21

&lt;211&gt; 682

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (624)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 21

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gctcttcctt	ttgaagcctg	atccagtatg	catttggagc	taattactgc	agttgacaca	300
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&lt;210&gt; 22

&lt;211&gt; 770

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 22

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aacaatagta	aaccttgatc	cacagatcac	atgtgccatt	ggataaaaat	aaataatgca	660
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&lt;210&gt; 23

&lt;211&gt; 565

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (10)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (21)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

<221> SITE  
 <222> (538)  
 <223> n equals a,t,g, or c

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 aatgaatata ttttatattta tgtaaattat acctcaaagt tgaatttttt taaaaagttt 240  
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 <211> 1356  
 <212> DNA  
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 gccctctctt gcttatatgt cttgtattga tatttggact ctgtatatac aatactataa 780  
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 gctattcccc attcacgccc ttttcagcag gaagtagcca gaaggagtgc cgcacaaaaa 960  
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 <211> 617  
 <212> DNA  
 <213> Homo sapiens

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&lt;210&gt; 26

&lt;211&gt; 648

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 26

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&lt;210&gt; 27

&lt;211&gt; 1388

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 27

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 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (17)  
 <223> n equals a,t,g, or c

<220>  
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 <222> (580)  
 <223> n equals a,t,g, or c

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 <213> Homo sapiens

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 30

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&lt;210&gt; 31

&lt;211&gt; 789

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 31

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&lt;210&gt; 32

&lt;211&gt; 884

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 32

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 <213> Homo sapiens

<400> 33						
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&lt;210&gt; 35

&lt;211&gt; 1215

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 35

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&lt;210&gt; 36

&lt;211&gt; 1794

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1675)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 36

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&lt;210&gt; 37

&lt;211&gt; 1174

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 37

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&lt;210&gt; 38

&lt;211&gt; 1087

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

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&lt;222&gt; (408)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1005)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 38

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&lt;211&gt; 438

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 39

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&lt;211&gt; 734

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 40

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 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (707)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (998)  
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gccggggcg	gtggatcacc	tgaggtcggg	agttcgagac	ccgtctaacc	aacatggaga	660
aacctgctt	ctactawaaa	tcacaaaatta	gccagggtatg	gtggcanatg	cctgttacc	720
cagctgcttg	ggaggctgag	gcaggagaat	tgcttgagag	gcagagggtg	ttgtaagccg	780
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aaaagaaaag	ggctgcctgg	gtccctggga	agacccagct	cccctctgta	tcctagccaa	900
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gtgggtgggg	gtgggggtcc	tgagctcac	ttctgtgntc	gcgtaataag	ggagagatca	1020
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tggtgtgtgt	tttttctttt	tcttctctc	cttctccttc	ttcttctctt	ctccttcttt	1140
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cggttactg	caacctccac	ctcctgaggt	caggagaatt	gcttgagagg	cagagggtgt	1260
tgtaagccga	gatcgcgcca	ttgcacgcca	gcctgggcaa	caagattgaa	actcccatct	1320
caaaaaaaaa	aaaaaaaaaac	tcgtag				1346

<210> 42  
 <211> 998  
 <212> DNA  
 <213> Homo sapiens

<400> 42

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gagccaagag	gggacgtaac	cacttgccag	tgtggcccag	tatttatatg	gtagaagctc	120
gggctggcag	tgagatggag	gtgggaaaga	ggagggtgtc	tcgtgtttaa	agatttctct	180
cttgtgtggg	ccttggttat	ggctcccat	gggtgcttgc	gctcccttgg	tcgcctttcc	240
ttgcattttg	ctttttgect	ttagtccctc	tgcagtcagg	gaccatgttg	gtgactctcg	300
gtcagatgtt	cccatatttg	catgtcttgc	tttggcctct	ctggctctag	gttctgtatt	360
gctagtgtgt	ttctgacatt	ttttctcatt	gtttgtgcta	ccttggccaa	gaacctcttt	420
gccttctccc	tcgtttgtaa	cattgagatc	ctagtagcag	ttacttctta	gggttggttag	480
gatgacatga	gatgggagag	ttggccatct	gccacacaag	agttcccttc	tcactgccat	540
cctctgcca	gggtgttccc	cagaatctgc	agggcccat	tggatcatct	gctgtctgca	600
caccttcttc	tctcacctct	tggcacttcc	ctcaaaaaag	agagaagtgg	agcacagtaa	660
ataaacgcca	gcgtttttct	cagttcccat	cacctctccg	gaactggatc	ccccaaactc	720
ctctgtcact	ttctgtgtcc	agcgggcccc	tggggtcctt	cactgtcttc	actctgtctc	780
gcctgtgcgc	ttggccttgg	tgctgtaggg	actgttataa	gagctgctgt	ccgatcccca	840
tattcaatct	cacagcccca	ctttgtgtac	acacaccaga	gccatcttct	taaaatcaga	900
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taaaaaaaa	aaaaaaaaa	aaaaaaaaa	aaactcga			998

<210> 43  
 <211> 658  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (6)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (15)  
 <223> n equals a,t,g, or c

<400> 43						
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aagccttgat	attgatactg	ctaaatctat	gttagctctt	ctgcttgga	ggacatggcc	180
actgttttca	gtattttacc	agtacctgga	gcaatcaaag	tatcgtgtta	tgaacaaaga	240
tcaatggtag	aatgtattag	aattcagcag	aacagtccat	gctgatctta	gtaactatga	300
tgaagatggg	gcttggcctg	ttcttcttga	tgaatttggt	gagtggcaaa	aagtccgtca	360
gacatcatag	caagaactat	gtgaagaaaa	tgcaaacctt	tcaattccca	cgtgtataca	420
agctaagtgt	atgaggggga	aaaaaatcca	acgggtgcat	tttcattcat	atgaaagact	480
tctcatagta	cttttttttc	ctttttttta	aggaggtttt	tcttggtaca	tgtgatgggc	540
attgagccac	acctcttctt	agactgaata	ttgaagtgtt	tgttttgagt	tatgtttata	600
acattttatt	cagaacaata	aagattcaga	tttgtgacaa	aaaaaaaaa	aaaaaaaaa	658

<210> 44  
 <211> 566  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (68)  
 <223> n equals a,t,g, or c

**SUBSTITUTE SHEET (RULE 26)**

<400> 44  
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 aagttctcct cctgatacaca gccatcttgg cagtggctgt tggtttccca gtctctcaag 180  
 accaggaacg agaaaaaaga agtatcagtg acagcgatga attagcttca gggttttttg 240  
 tgttccctta cccatatcca ttctgcccac ttccaccaat tccatttcca agatttccat 300  
 ggtttagacy taattttcct attccaatac ctgaatctgc ccctacaact ccccttccta 360  
 gcgaaaagta aacaagaagg aaaagtcacg ataaacctgg tcacctgaaa ttgaaattga 420  
 gccacttcct tgaagaatca aaattcctgt taataaaaga aaaacaaatg taattgaaat 480  
 agcacacagc attctctagt caatatcttt agtgatcttc ttaataaac atgaaagcaa 540  
 aaaaaaaaaa aaaaaagggs ggccgc 566

<210> 45

<211> 1277

<212> DNA

<213> Homo sapiens

<400> 45  
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 acatgtaaca ggggagcaga aggagggata aatgatttgt ttatgctcaa taaagatgtt 120  
 gctgctgttc tgtcagctaa cctttgctct cataacctgc ataaacttgc aaagtcttta 180  
 tttattctcc taccagcaaa ttattggaat tcatagtcac gtctaatttt agtttagctta 240  
 gggatggcac tcaacagggt tataaaaggg ggagaacatc tctctcattc ctgaatttcc 300  
 aaggctggga ttacggtaaa gctgtgggag atcacagtaa ttgaggtttc ccaggacact 360  
 cccatagtgg gttatgcttc ccaaactctgg ctttctaagc ataatggaat ctggcctaac 420  
 ctgtcttcca atatttgagt ctcttctata gcacctctgt cagagtgggt tgtgttcttc 480  
 acttgataaa aacttttttg gggatgcac attacagttt gagccagggtg atttcatctt 540  
 caggcagctg tgatagataa taatacacaa taaggaaaca acgaaacact ttttaatgga 600  
 ttagtaagtg ggaatagata gggcacctgt catttcattg ttgtccgcat gacctgatga 660  
 ggtagttaac tgtagtgct acttccattt tcaggccaaa aactgggggc ttggaatagt 720  
 ggagcaactc cggcagtgcc acacagctat gaaatatcag gtcagaaccc cagggatact 780  
 ggatccaaaa acctgagagg aagctatata tcctttaact tcttcacca aagctgaaat 840  
 ctgcttccta gttctatcct ccaatgacct aaggaaaaga atctcttcg ctacttgctc 900  
 ttcagatatt taacacaact ttcaggcctt cttttgcatt cttttcaggc cacaggacac 960  
 tgtttttcgg tgttcgttcc cccaaccccc ccaaaccacg tatttttctc atttggtta 1020  
 ttgcagtagc tctctaaagg tctgcctgct ctgttcccta ttcttcaccc agcagccaag 1080  
 gccacgctta aaatacaagt caaatcactt cattcctctg ctcagaacac ttctgcagtt 1140  
 ttctctgtca cttgaggtaa aaccttaagt caacttgaag attacagaat tgaattgtct 1200  
 tactgaaatt acctttccaa aatcgatggg tcccaactcg tgccgaattc gatatcaagc 1260  
 ttatcgatac cgtcgac 1277

<210> 46

<211> 442

<212> DNA

<213> Homo sapiens

<400> 46  
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 tttcatgtgg ctgagaggga tccatccttt cctgtggctg agcgggatcc attccttccc 120  
 gtggctgagt ggaggcccat ccttaggtac ctccagttag cagccacat ccttgaggga 180  
 tggaaaattg atttgectct tcacagactt ctctggttct agctttgggc tatttatgctg 240  
 tgaagctgct aagaacattt cccaaatgtg atttgtataa atacctagga gtaggattcc 300  
 tagtgtgagg tcagagtctg tctagcagca taaaaacaac caaaagattt tctgagctc 360  
 agggcacatg ggtggggccc agagagcacc caggaccgaa gctgccagg acctccctcg 420

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aggggggccc gtaacccatt cg

442

<210> 47  
 <211> 890  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (818)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (819)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (829)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (859)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (887)  
 <223> n equals a,t,g, or c

<400> 47	
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tgagctacaa caaaaggact tcaggaacaa gtaatgtatt agtatgggtc aagattggtg	120
ataggaaactg tctcaaaagg atggtgggta ttttaaatat aaatagctaa tgggggtggg	180
aggcctataa aattaaatgc cttgtataaa atccaaaatg aatgcaaaat tgttttcact	240
tgtattgact ttatgttgta tgattccaat ctctgttctg tttggcactt gtatttaatt	300
cttcaccttt gtaagacatt tgtatattgt ggatgtgttc attcaagcta tttaatatct	360
ggcactgtta atacacagta ctttattgta cagactgttt tactgtttta attgtagttc	420
tgtgtacttt ttttggatgg ggctggcatg ttttctttgt ttcttggaac tacgacgtgg	480
gaatttcaat gcgttttgtt gtagatgcta acgtgtcaga atcctttaca ttcaactttt	540
ctaagaaaag ctttttcagt cttgtagtgt gtgcttacag taactaattt tgttgaaaat	600
ggtttcaagt tattcaaat tgtacaggac tgtaaagatt tgttgacagc aaaatgttga	660
agaaaaaagc ttatagaata aaagctataa agtatatatt aggatctgca aacaatgaag	720
aattatgtaa tatattgtac aaatgtaagc aaaggctctg aaataaaatg ccatagtttg	780
tgaaaaaaaaa aaaaaaaaaa actcgagggg gggcccgnaa cccaatcgnc caaaagttag	840
tcgtattaca attcactgng ccgtcgttta caacgtcgtg actgggnaaa	890

<210> 48  
 <211> 737  
 <212> DNA  
 <213> Homo sapiens

<220>

**SUBSTITUTE SHEET (RULE 26)**

<221> SITE  
 <222> (736)  
 <223> n equals a,t,g, or c

<400> 48  
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 cgctggctcg cgagtagca agtggccatg gggagcctca gcggtctgcg cctggcagca 120  
 ggaagctgtt ttaggttatg tgaaagagat gtttctcat ctctaaggct taccagaagc 180  
 tctgatttga agagaataaa tggattttgc aaaaaaccac aggaaagtcc cggagctcca 240  
 tcccgcaatt acaacagagt gcctttacac aaacctacgg attggcagaa aaagatcctc 300  
 atatggtcag gtcgcttcaa aaaggaagat gaaatcccag agactgtctc gttggagatg 360  
 cttgatgctg caaagaacaa gatgcgagtg aagatcagct atctaattgat tgccctgacg 420  
 gtggttaggat gcatcttcat ggttattgag ggcaagaagg ctgcccagg acacgagact 480  
 ttaacaagct tgaacttaga aaagaaagct cgtctgaaag aggaagcagc tatgaaggcc 540  
 aaaacagagt agcagaggta tccgtgttgg ctggattttg aaaatccagg aattatgtta 600  
 taacgtgcct gtattaaaaa ggatgtggtg tgaggatcca ttccataaag tatgatttgc 660  
 ccaaacctgt accatttccg tatttctgct gtagaagtag aaataaattt tcttaataa 720  
 aaaaaaaaaa aaaaanc 737

<210> 49  
 <211> 571  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (249)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (548)  
 <223> n equals a,t,g, or c

<400> 49  
 tcgaccacag cgtccggggg cgtacgcggg caagatggag gcgactacgg ctggtgtggg 60  
 ccggctagag gaagaggcgt tgcggcgaaa ggaacggctg aaggccctac gggagaaaac 120  
 cgggcgcaag gtgagaagtg tggagtgagg gtcgcagttg aggcgtccag cggtcggggg 180  
 ccgggtcgcg cttgaggaga gcaaagggct aataaggaaa gacagctgcc gagggcgcg 240  
 atgccgggnc gctaacgcat gcgcgagaag acgggcgccc tcccacgatg tctggggctg 300  
 cttggcggtg gactcctctg gcgctggtgc ggtcgtcgcg cacgcgcggg ggtgggcaar 360  
 gcatggtcag cgaccgcag tccatctgac tcctgcttcc cgggtgttgc tcgtgtaggt 420  
 atctagggct gcctgtaggt tcagatgctt gttgggttag gcgtgatttg ttccgttcct 480  
 ctatggccta gctggtcttt aacccccgcc ttcgattctg agtcagacag actccccagt 540  
 tcgggacangc aattcccttg gaacaagggc a 571

<210> 50  
 <211> 356  
 <212> DNA  
 <213> Homo sapiens

<400> 50  
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 tccctccctc cctctctact ctctccctt ccttcaggcc tcttagcatt gttgttttc 120  
 ccatttctga tactactact ccatgctgaa gatttgccat attactattt tggaaacatt 180

**SUBSTITUTE SHEET (RULE 26)**

gagtgataga	actcctagaa	aatttgcaaa	gaaatgttac	atactgtata	tcaaactctc	240
agattctagt	gttgaaaaag	tagcctatac	tttgctatta	cttatacctg	ctgccataga	300
aaaaaataa	gtttattcat	gacacattta	catttgatca	taaaaaaaaa	aaaaaa	356

<210> 51  
 <211> 913  
 <212> DNA  
 <213> Homo sapiens

<400> 51

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tcatgttatt	cacttattca	tatgtgggaa	tgaacagttc	agccagtata	aaggacaggt	120
gagtacacac	caaggagatc	ttcagggaga	gatcagctgg	ttttcctgtg	aagatgtcag	180
cttcatccct	ccaccgtctc	cctgtgctca	tggctctgtt	ccctttccag	gctgctgctg	240
ctggttcttt	gggtctgcag	ccacctccca	ccccatgaa	gggcaaacc	agcattatgt	300
tacctcctca	gtataaaagg	agagaggggtc	tcaaaaaaaa	aaaaaaaaaa	atccaaaaag	360
ttgctcttgt	cagctttggg	agggcagact	ccatagttgg	agatgggctt	ccaaccaacc	420
aaggagataa	atgccagagg	gagcgaacca	tgccaggctc	aaagcacatc	tctccccaaa	480
ctccccaggt	ggggaagcag	gccagagggt	ccacaaacc	ctcaggagg	cctggagtcc	540
agatgctgta	ctccagtatc	taaacaatca	ctgaatctta	aagctgacag	gttcaaagct	600
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tgggtggatc	acctgaggtc	aggagtttga	gaccaacctta	gccaaatgg	tgaaaaccca	720
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ctcggtaggc	tgaggcagaa	gaatcgcttg	aaccaggag	gcagaggttg	cagtgagctg	840
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aaaaaaaaaa	aaa					913

<210> 52  
 <211> 1356  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1231)  
 <223> n equals a,t,g, or c

<400> 52

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aactctgtca	accagggtgca	gaaaatgctt	ttaaagtgg	acttagtata	agaacagctc	120
tgggagataa	agcatatgcc	tgggatacca	atgaagaata	cctcttcaaa	gcgatggtag	180
ctttctccat	gagaaaagtt	cccaacagag	aagcaacaga	aatttcccat	gtcctacttt	240
gcaatgtaac	ccagaggtat	cattctgggt	tgtggttaca	gacccttcaa	aaaatcacac	300
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ggatgagagg	ctcacccctc	tctgaagggtc	tgtgtgtctg	cttcctcaag	aaattaaaca	720
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taccaccaa	caccactgaa	atcataagct	attcagcact	caaaatattc	taaaatattt	900
ttctgacagt	atagtgtata	aatgtgggtc	tgtggtattt	gtagtatttg	atttaagcat	960
ttttagaaat	aagatcaggc	atatgtatat	attttcacac	ttcaaagacc	taaggaaaaa	1020

taaattttcc	agtggaggat	acatataata	tggtgtagaa	atcattgaaa	atggatcctt	1080
tttgacgac	acttatata	ctctgtatat	gactaagtaa	acaaaagtga	gaagtaatta	1140
ttgtaaatgg	atggataaaa	ttggaattac	tcataacag	ggtagggattt	tatcctgtta	1200
tcacaccaac	agttgattat	atattttctg	nataatcagcc	cctaatagga	caattctatt	1260
tgtagaccat	ttctacaatt	tgtaaaagtc	caatctgtgc	taacttaata	aagtaataat	1320
catccaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaa			1356

&lt;210&gt; 53

&lt;211&gt; 1547

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 53

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actccgatgt	cgacgagttt	ctggacaatt	tctcatgctg	gcgtgaagca	gagtgcacct	360
cccagaaagg	agacggagca	gccgcctgcg	ccggggggagc	atggaggaga	gcgtgagagg	420
ctacgactgg	tccccgcgcg	acgcccggcg	cagcccagac	cagggccggc	agcagggcga	480
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cccgcccgc	tcggcgcgcg	aggccttccg	cgtggtgctc	aagggtgtct	tcgccaactt	1020
catccagtac	ctgctggacc	cgcacacgga	gaagctggcg	cccttcaacg	agcactggcg	1080
gcaggtgtac	cgccctctgcc	accctgtcca	gatcgactac	gattcctggg	gaagctggag	1140
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&lt;210&gt; 54

&lt;211&gt; 1338

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 54

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&lt;210&gt; 55

&lt;211&gt; 2071

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 55

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<210> 56  
 <211> 1899  
 <212> DNA  
 <213> Homo sapiens

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 <221> SITE  
 <222> (1439)  
 <223> n equals a,t,g, or c

<400> 56

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 <211> 1543  
 <212> DNA  
 <213> Homo sapiens

<400> 57

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&lt;210&gt; 58

&lt;211&gt; 1133

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 58

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&lt;210&gt; 59

&lt;211&gt; 1490

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 59

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&lt;210&gt; 60

&lt;211&gt; 1336

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 60

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 <211> 1705  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (779)  
 <223> n equals a,t,g, or c

<400> 61  
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 <213> Homo sapiens

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&lt;210&gt; 63

&lt;211&gt; 1589

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 63

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&lt;210&gt; 64

&lt;211&gt; 1088

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 64

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&lt;210&gt; 65

&lt;211&gt; 1256

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1079)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 65

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&lt;210&gt; 66

&lt;211&gt; 1602

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 66

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&lt;211&gt; 938

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 67

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&lt;210&gt; 68

&lt;211&gt; 1585

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

SUBSTITUTE SHEET (RULE 26)

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 <223> n equals a,t,g, or c

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 <212> DNA  
 <213> Homo sapiens

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&lt;211&gt; 1344

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 70

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cttgcttgtg	aatgtttcct	tcattctccag	gttgtctggg	gacaattctg	tcttttggag	420
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tgggggaaaa	aggaatgaga	aaaacaaaca	caagaaggca	aaacaaaaac	acctggttca	780
attaaaaaca	acaacaaagc	aaaacaaaaa	aaacccaaaa	caaaccaca	caataaatga	840
gaaaaaaatt	acataaaaca	gatgacatgt	atagaaataa	aaaaatagaa	tggaggaact	900
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acactggatt	aaaaaacaaa	tccaggggaat	acagttcaca	gctgatata	tcaaaatata	1020
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cgagatcgcg	ccactgcact	ccagcctggc	aacagagtga	gactctgtct	caaaaaaaaa	1320
aaaaaaaaaa	aaaaaaaaaa	aaaa				1344

&lt;210&gt; 71

&lt;211&gt; 1474

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 71

ggcagcagct	aaaatatgct	taaagtaaga	tgtttctatg	ttatgtggtt	atgttatcaa	60
taatatattg	ttgatcttca	catattttat	atgcatatat	atatcaagaa	gttatatata	120
tataactcaa	gaaactcaag	ttatatatat	atgtcaagaa	atgtatgatt	attttggaga	180
gaatgggccc	aaatgtgaaa	aagatatata	aaaaacaaaa	aaaacaaaaa	aaaaacacta	240
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cttacaacaa	gtactgtcaa	acctcaaatg	ctttctttct	tcagatgctt	tttcgtgtac	480
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cataaataga	aagaaaaata	atctagaaat	ttttcaaagc	tagtactctt	tctccttata	720
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catctttcag	taaagtcttg	tcagaaaaaa	attgtctgat	aaatatggaa	aaataaaaatt	1440
tgaattttag	ttaaaaaaaa	aaaaaaaaaa	aaaa			1474

&lt;210&gt; 72

&lt;211&gt; 2012

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1468)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 72

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tatacccttt	ctgcttttcc	ccaagcctct	tgcactaata	acgttctgta	ccagagtggg	120
atgtttgtta	caatcagtga	acctagactg	gacacctcat	tatcacccaa	gaccaagggt	180
tacgttaagg	ttcgctctta	gtggtgtata	ttctatgagt	ttgacaaatg	tttaattgaca	240
tgtatccacc	atgatagtat	catacagaat	agtttactct	ccttctctctg	tgctctgcct	300
gttcatccct	cccttccctg	tgatcttcta	ttgtctccat	agttttgtct	tttcccaaat	360
gctgtatagt	tgggaattatc	atgtaacctt	tcaaatggcc	ttttcactta	taatatgcgt	420
ttaagggttt	ctacagtctt	kgcaggcttg	atagctcatt	tttctttagt	gctgaatact	480
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cataagtttt	caactcattt	gggtaaatac	caagcagcac	aattgccgtg	ttgtatagta	660
agagaatggt	tagtttcata	agacatcacc	aagctgtctt	acaaagtggc	tgtactattt	720
tgactttcca	ccagcaatga	atgagagttc	ttgttggttc	cacatactcg	tcagcatttg	780
atgatatcag	tgtttttagat	tttgaccatt	taataggtgt	gtagtggcat	ctccttggtg	840
ctttaacttg	taattctcta	atgacttata	atgttgagca	tcttttcata	tacttatttg	900
ccatttgtgt	ttcttcttcc	tttttctttt	tctttttctt	tttttttttt	tttttttgag	960
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tgcttacctt	aaactgtata	caaaaattac	ctcaaaaaag	atcgaagtcc	taaatgtaag	1380
acctaaaact	ataaaactct	tagataaaaa	cataggagga	cattggattt	ggcaatggat	1440

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gggctgcagc		gggctgtgat	tgtgmcgctg	cactccggcc	tgggcaacag	agggagaccg	1980
tgtctgaaaa		aaaaaaaaaa	aaaaacctcg	ag			2012

&lt;210&gt; 73

&lt;211&gt; 1267

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 73

ggcacgagct	cactctagct	gctatgataa	acaagaagac	cagtgaggaa	gttttgaaac	60
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gtgggaagtg	ggctcagccc	agggactgcc	tttggatccc	ccagcattgg	caccatacct	180
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cactgtaggg	cgtgaggggt	gagtagctgc	tggcctccaa	gtccatagct	actcatgttg	480
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aattgggggt	acaagcgatg	aaaagagggt	caacatcact	aatcactagg	gaaatgcaaa	1200
tgaaaatcat	aaggaggtac	cactttgtac	ccttaaaaat	agttactaca	aaaaaaaaaa	1260
aaaaaaa						1267

&lt;210&gt; 74

&lt;211&gt; 1748

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 74

ggcacgagta	aagacaaaat	aaattcttct	gtccacttat	ttacctaaca	tacacttgct	60
tccttggaag	tcataggcat	ccacatatct	tcagccacaa	cttggtatct	ctaataataat	120
tcttattttt	gaactcctaa	actttctggg	agaaatcttc	agttgaaaat	atcctggcaa	180
gtaaaattag	aaactcccag	aaatgtactt	atttctatta	tgtgttttta	tttctgaaca	240
ttgtgcccac	cattcttttc	cacatacttg	cccaaattgg	aaaactaggg	ttctaagttt	300
ccccctccat	ccatgcccac	atttaattca	ccctaataat	acctgacatc	tttcaagttc	360
attttctact	atctatcccc	acgcaggcca	tatctgggtt	gaagcttcat	tatctctata	420
gatttaaaaac	tcaatacaaa	caaaaacaaat	aacatacaaa	caaaaaccac		480
ctaactcatc	tttatgtagt	cagtcctccc	tcaatagttt	ggccaaactt	cctaaaccga	540



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aaagaccatc	acaattgctg	atataacttt	aataaaatct	gcaacatttt	cagatggaag	1440
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aatatcaaga	tcacaataat	cacttaaaat	agttacatat	gtaactaacc	tgacacaatgt	1680
gtacatgtac	cctaaaactt	aaagtataat	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1740
aaaaaaaaa						1748

&lt;210&gt; 75

&lt;211&gt; 1570

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (7)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (8)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (10)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 75

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aaagtagctt	cagaacccaa	caaaaattat	gtaagcctgg	ttaaatgtcc	ttttttcttc	720
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40

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gggcgggcgc						1570

&lt;210&gt; 76

&lt;211&gt; 524

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 76

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gcccgggtgtg	ttggcaacaa	ctggatctga	agatggcagt	cagggtgctt	tggggtgggtc	180
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&lt;210&gt; 77

&lt;211&gt; 1306

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 77

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ggaccaaggg	acccaccatc	agtgtgcttg	ttgagatgtg	ctcatctttt	ccaagaatgg	720
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agcctttcct	ctggaggtcc	cctggaagcc	agtgtttgct	gtgtctccag	accatccatg	840
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gtttcctcca	gaagagctat	cggaaagctg	agaagaaccc	agagaaggag	gaggagcact	1020
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tcttgtcaga	accctcaggc	agggcagatg	tgtcaccaaa	taaaac		1306

&lt;210&gt; 78

&lt;211&gt; 1479

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 78

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&lt;210&gt; 79

&lt;211&gt; 1794

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 79

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&lt;210&gt; 80

&lt;211&gt; 1280

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 80

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&lt;210&gt; 81

&lt;211&gt; 974

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 81

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aaaaaaaaaa	aaaa					974

&lt;210&gt; 82

&lt;211&gt; 1955

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 82

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 <211> 638  
 <212> DNA  
 <213> Homo sapiens

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 actttctcgt aaaagttaaa aaaaaaaaaa aaaaaaaa 638

<210> 84  
 <211> 859  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (27)  
 <223> n equals a,t,g, or c

<400> 84  
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 aaaaaaaaaa aaaaaaaaaa 859

<210> 85  
 <211> 1129  
 <212> DNA  
 <213> Homo sapiens

<400> 85  
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**SUBSTITUTE SHEET (RULE 26)**

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&lt;210&gt; 86

&lt;211&gt; 2674

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2607)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2611)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2621)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2634)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2650)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2660)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2669)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 86

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&lt;210&gt; 87

&lt;211&gt; 1636

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

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&lt;222&gt; (1624)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 87

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cggnggcaag	ctggac					1636

&lt;210&gt; 88

&lt;211&gt; 1639

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (12)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 88

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gtcaggcggg	ccgtgggttc	ccggaggggs	tcttgaggcg	ccatttcaag	tcgccccag	120
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gtggagcctg	ggcttcacag	tgacactcac	gtttgaactc	ccggtcggct	gtgtgcttgg	240
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cccctgcagg	accgagatga	tgtccaatga	caagccctgg	cttccagcca	atgctcctgc	360
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&lt;210&gt; 89

&lt;211&gt; 1860

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1846)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1848)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1853)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 89

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&lt;210&gt; 90

&lt;211&gt; 839

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 90

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&lt;210&gt; 91

&lt;211&gt; 1145

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (386)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 91

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cctgt						1145

&lt;210&gt; 92

&lt;211&gt; 2050

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (515)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 92

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 aaaactcgag 2050

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 <211> 1173  
 <212> DNA  
 <213> Homo sapiens

<400> 93  
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 ggctcagagca tctcgtgtt tttttgttgt tgttttaaaa tattatgatt tggctacaga 180  
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 ctttgatggt ctggtgccag tgctgtgcc cactctgtgc ctgctgggag gagggcccagg 360  
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&lt;213&gt; Homo sapiens

&lt;400&gt; 95

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&lt;210&gt; 96

&lt;211&gt; 2092

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (637)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 96

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&lt;210&gt; 97

&lt;211&gt; 1352

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 97

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&lt;211&gt; 913

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 98

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&lt;210&gt; 99

&lt;211&gt; 721

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 99

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&lt;211&gt; 645

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 100

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&lt;211&gt; 563

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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&lt;210&gt; 104

&lt;211&gt; 1466

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 104

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 <212> DNA  
 <213> Homo sapiens

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 <211> 1516  
 <212> DNA  
 <213> Homo sapiens

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&lt;210&gt; 107

&lt;211&gt; 1689

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 107

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&lt;210&gt; 108

&lt;211&gt; 1943

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (161)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1926)

SUBSTITUTE SHEET (RULE 26)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1928)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1934)

<223> n equals a,t,g, or c

<400> 108

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<210> 109

<211> 1594

<212> DNA

<213> Homo sapiens

<400> 109

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&lt;210&gt; 110

&lt;211&gt; 1742

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 110

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&lt;210&gt; 111

&lt;211&gt; 1501

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 111

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&lt;210&gt; 112

&lt;211&gt; 791

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 112

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&lt;210&gt; 113

&lt;211&gt; 1637

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 113

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&lt;210&gt; 114

&lt;211&gt; 1588

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (778)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1150)

&lt;223&gt; n equals a,t,g, or c

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&lt;400&gt; 114

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&lt;210&gt; 115

&lt;211&gt; 1926

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 115

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&lt;210&gt; 116

&lt;211&gt; 1063

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 116

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&lt;210&gt; 117

&lt;211&gt; 1615

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 117

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&lt;210&gt; 118

&lt;211&gt; 1221

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (697)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (700)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (701)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (712)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (720)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (722)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (742)

&lt;223&gt; n equals a,t,g, or c

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<210> 119

<211> 1149

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1120)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1140)

<223> n equals a,t,g, or c

<400> 119

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cagaaaattg acctatgtaa tgaaatacta gaagaaaact ctaaaattaga atggctttgt 180  
tatgaatttt taatgataag tactaacact taaaaggga aaaattttct aaagaaaatg 240  
cctaaaaatg tgttgatct gagatcatca tatatgtagt attacagtgc aaacactatt 300  
aatgttaatg aggtaggtgg atttttttaa tgaaaaaact tgaaatatta tcaggttgct 360  
ccatttatg gaatttaagc ttgtcagaaa gatccagata gctatattaa tattttatct 420  
gtatttggtt gcggttgctt taaaaataa gttttcttat aagtcatttc aattttttgg 480  
tttagagtcc atatttcaaa ataaaaagtt aaaaaaagag taccttatgt aatttagcaa 540  
ggtattccat aaactcaggg agggaaaaaa aaaaactaag atgagaggct agttataatg 600  
atctttattt atatattgca ggaaatgatt tctctctca caacttagca taatttactg 660  
ctaataattt tagccatggg ttgaaaaaaa ttaartgggt ttgtaagtgc taatcctttg 720  
ttactcattt aaactggtaa aatgtagtcc ccgctcctg aggaggacct gtccaaactc 780  
ttcaaacac ccagccgcc tgccaggatg gactcgctgc tcattgcagg ccagataaac 840  
acttactgcc agaacaatcaa ggagttcact gcccaaaact taggcaagct ctctatggcc 900  
caggctcttc aagaatacaa caactaagaa aagggaagtt ccagaaaaga agttaacatg 960

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aactcttgaa	gtcacaccag	ggcaactctt	ggaagaaata	tatttgcata	ttgaaaagca	1020
cagaggattt	ctttagtgtc	attgccgatt	ttggctataa	cagtgtcttt	ctagccataa	1080
taaaataaaa	caaatcttg	aaaaaaaaa	aaaaaaaaa	ggsgggccgc	tctaaggggn	1140
tccaagctt						1149

&lt;210&gt; 120

&lt;211&gt; 1515

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (69)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 120

aattcggcac	gagggaaatt	caagcacttt	tcctaaaaga	agggggaatg	gatgctgaaa	60
caacacgtnt	cccacaaagg	gagcagacac	tggtctgtg	aagctgcccc	ataccttccc	120
cacagaactg	gggtccggcc	tcctgacat	gcagatttcc	acccagaaga	cagagaagga	180
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ccgtttcagc	ctggccagcc	ctctggaccc	cgaggttggg	ccctactgtg	acacacctac	300
catgcggaca	ctcttcaacc	tcctctggct	tgccctggcc	tcagccctg	ttcacactac	360
cctgtcaaag	tcagatgcca	aaaaagccgc	ctcaaagacg	ctgctggaga	agagtcaagt	420
ttcagataag	ccggtgcaag	accggggttt	ggtggtgacg	gacctcaaag	ctgagagtgt	480
ggttcttgag	catcgcagct	actgctcggc	aaaggcccgg	gacagacact	ttgctgggga	540
tgtactgggc	tatgtcactc	catggaacag	ccatggctac	gatgtcacca	aggtctttgg	600
gagcaagttc	acacagatct	caccgcgtctg	gctgcagctg	aagagacgtg	gccgtgagat	660
gtttgaggtc	acgggcctcc	acgacgtgga	ccaagggtgg	atgagagctg	tcaggaagca	720
tgccaagggc	ctgcacatag	tgctcggct	cctgtttgag	gactggactt	acgatgattt	780
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aaaaaaaaa	aaaaa					1515

&lt;210&gt; 121

&lt;211&gt; 1025

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 121

ggagaattgt	tactgggtgaa	ttggttttca	ggttttgagc	atacatatac	aatgtgtttc	60
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tacaaatagg	ttttcttaaa	ccagagatgc	actgcccttg	tctaaagttc	ttattgcact	180
ggtttatatg	tgtatgtgtg	ttttattgtg	tggtttttta	atttgtaagt	attctaagag	240
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gttatgaacc	ttggggcatt	aaaatcccat	ggcaaggagc	ataagagatg	ttctcgtagc	960
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tcgag						1025

&lt;210&gt; 122

&lt;211&gt; 2207

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 122

ggcacgagca	cgaatcagct	gcaggctctct	gttttgaaaa	agcagagata	cagaggcaga	60
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cagaagccct	gttcatgggt	ggggatattt	tctcgactgc	atggaatcag	aaagaagcaa	180
aaggatggga	aatgcctgca	ttcccctgaa	aagaattgct	tatttccctat	gtctcttatt	240
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<210> 123  
 <211> 1770  
 <212> DNA  
 <213> Homo sapiens

<400> 123  
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 ctctgatctg cagagctcca ggacacctgg ggtctggaag gcagaggctg aggacaccag 180  
 caaggacccc gttggacgta actggtgcc ctacccaatg tccaagctgg tcacctact 240  
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 ccagactgcc agaaagtcaa agtcatgtac cgcattggccc acaagccagt gtaccaggtc 360  
 aagcagaagg tgctgacctc tttggcctgg aggtgctgcc ctggctacac gggccccaac 420  
 tgcgagcacc acgattccat ggcaatccct gagcctgcag atcctggtga cagccaccag 480  
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 gcaggccagg ctggggccagc tgcagaggaa cctctcagag ctgcacatga ccacggcccg 1200  
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 cctgatggag aagtctctga tcatggagga gaacaaggag gaggtggagc ggcagctcct 1440  
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 gaaggactgc aattgccaga agctctatct agacctggac gtcattccggg agggccagag 1560  
 ggacgccacg cgtgccctgg aggagaccca ggtgagcctg gacgagcggc ggcagctgga 1620  
 cggctcctcc ctgcaggccc tgcagaacgc cgtggacgcc gtgtcgctgg ccgtggacgc 1680  
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 ggcgctggat gacgaggtgg gcgcgctgaa 1770

<210> 124  
 <211> 1034  
 <212> DNA  
 <213> Homo sapiens

<400> 124  
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 cccagggggc tggggcccagg gccatgtccc acccggctgc agccaaggcc tcaacccct 180  
 gtactacaac ctgtgtgacc gctctggggc gtggggcatc gtcctggagg ccgtggctgg 240  
 ggcgggcatt gtcaccacgt ttgtgctcac catcatcctg gtggccagcc tcccctttgt 300  
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 caccaggcgg ccacaccgcc gaaagacggc aagaactctc aggtcttttag aaaccctac 600  
 gtgtgggact gagtcagcgg tggcgaggag ayycggtcgg atttggggag ggcctgagg 660

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```

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tgctcctctg tgaggaacaa ggggtgcctaa taaatacatt tctgctttat taaaaaaaaa 1020
aaaaaaaaaa aaaa 1034

```

&lt;210&gt; 125

&lt;211&gt; 353

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (353)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 125

```

Met Leu Cys Arg Leu Cys Trp Leu Val Ser Tyr Ser Leu Ala Val Leu
  1              5              10              15

```

```

Leu Leu Gly Cys Leu Leu Phe Leu Arg Lys Ala Ala Lys Pro Ala Glu
      20              25              30

```

```

Thr Pro Arg Pro Thr Ser Leu Ser Gly Ala Pro Pro Thr Pro Arg His
      35              40              45

```

```

Ser Arg Cys Pro Pro Asn His Thr Val Ser Ser Ala Ser Leu Ser Leu
      50              55              60

```

```

Pro Ser Arg His Arg Leu Phe Leu Thr Tyr Arg His Cys Arg Asn Phe
      65              70              75              80

```

```

Ser Ile Leu Leu Glu Pro Ser Gly Cys Ser Lys Asp Thr Phe Leu Leu
      85              90              95

```

```

Leu Ala Ile Lys Ser Gln Pro Gly His Val Glu Arg Arg Ala Ala Ile
      100              105              110

```

```

Arg Ser Thr Trp Gly Arg Trp Gly Asp Gly Leu Gly Pro Ala Leu Lys
      115              120              125

```

```

Leu Val Phe Leu Leu Gly Val Ala Gly Ser Ala Pro Pro Ala Gln Leu
      130              135              140

```

```

Leu Ala Tyr Glu Ser Arg Glu Phe Asp Asp Ile Leu Gln Trp Asp Phe
      145              150              155              160

```

```

Thr Glu Asp Phe Phe Asn Leu Thr Leu Lys Glu Leu His Leu Gln Arg
      165              170              175

```

```

Trp Val Val Ala Ala Cys Pro Gln Ala His Phe Met Leu Lys Gly Asp
      180              185              190

```

```

Asp Asp Val Phe Val His Val Pro Asn Val Leu Glu Phe Leu Asp Gly

```

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195	200	205
Trp Asp Pro Ala Gln Asp Leu Leu Val Gly Asp Val Ile Arg Gln Ala		
210	215	220
Leu Pro Asn Arg Asn Thr Lys Val Lys Tyr Phe Ile Pro Pro Ser Met		
225	230	235 240
Tyr Arg Ala Thr His Tyr Pro Pro Tyr Ala Gly Gly Gly Gly Tyr Val		
	245	250 255
Met Ser Arg Ala Thr Val Arg Arg Leu Gln Ala Ile Met Glu Asp Ala		
	260	265 270
Glu Leu Phe Pro Ile Asp Asp Val Phe Val Gly Met Cys Leu Arg Arg		
	275	280 285
Leu Gly Leu Ser Pro Met His His Ala Gly Phe Lys Thr Phe Gly Ile		
	290	295 300
Arg Arg Pro Leu Asp Pro Leu Asp Pro Cys Leu Tyr Arg Gly Leu Leu		
	305	310 315 320
Leu Val His Arg Leu Ser Pro Leu Glu Met Trp Thr Met Trp Ala Leu		
	325	330 335
Val Thr Asp Glu Gly Leu Lys Cys Ala Ala Gly Pro Ile Pro Gln Arg		
	340	345 350

Xaa

<210> 126  
 <211> 158  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (108)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (156)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (158)  
 <223> Xaa equals stop translation

<400> 126  
 Met Ser Trp Val Gly Leu Gly Arg Arg Gly His Leu Leu Leu Leu Ile  
 1 5 10 15

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Asn Pro Arg Ala Leu Ala Gly Ile Arg Leu Pro Ser Pro Thr Gly Ala  
                   20                                  25                                  30  
 Pro Ala Pro Gly Pro Cys Pro Pro Leu Cys Thr Pro His Cys Ser Arg  
                   35                                  40                                  45  
 Glu His Pro Ala Gly Gly Thr Gly His Pro Ala Gly Val Trp Trp Arg  
                   50                                  55                                  60  
 Arg Gly Cys Tyr Gly Gly Ser Cys Pro Met Gly Pro Val Arg Gly Ile  
                   65                                  70                                  75                                  80  
 Leu Gly Gly Leu Pro Cys Arg Glu Glu Ala Leu Arg Arg His His Ser  
                                   85                                  90                                  95  
 Lys Pro Cys Trp Arg Pro Gly Gly Gln Ala Arg Xaa Leu Gly Ser Trp  
                                   100                                  105                                  110  
 Pro Leu Thr Ala Gly Arg Glu Pro Pro Arg Thr Ala Ser Thr Ala Pro  
                   115                                  120                                  125  
 His Thr Ser Glu Pro Thr Ser Ser Phe Pro Arg Phe Pro Arg Ser Gln  
                   130                                  135                                  140  
 Ala Trp Glu Asp Leu Pro Asp Ala Ala His His Xaa Ser Xaa  
                   145                                  150                                  155

&lt;210&gt; 127

&lt;211&gt; 554

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (39)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (199)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (201)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (202)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (228)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

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&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (420)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (434)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (440)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (452)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (554)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 127

Met	Lys	Ile	Ala	Thr	Val	Ser	Val	Leu	Leu	Pro	Leu	Ala	Leu	Cys	Leu
1					5					10					15

Ile	Gln	Asp	Ala	Ala	Ser	Lys	Asn	Glu	Asp	Gln	Glu	Met	Cys	His	Glu
		20						25					30		

Phe	Gln	Ala	Phe	Met	Lys	Xaa	Gly	Lys	Leu	Phe	Cys	Pro	Gln	Asp	Lys
		35					40					45			

Lys	Phe	Phe	Gln	Ser	Leu	Asp	Gly	Ile	Met	Phe	Ile	Asn	Lys	Cys	Ala
	50					55					60				

Thr	Cys	Lys	Met	Ile	Leu	Glu	Lys	Glu	Ala	Lys	Ser	Gln	Lys	Arg	Ala
65					70					75					80

Arg	His	Leu	Ala	Arg	Ala	Pro	Lys	Ala	Thr	Ala	Pro	Thr	Glu	Leu	Asn
			85						90					95	

Cys	Asp	Asp	Phe	Lys	Lys	Gly	Glu	Arg	Asp	Gly	Asp	Phe	Ile	Cys	Pro
			100					105					110		

Asp	Tyr	Tyr	Glu	Ala	Val	Cys	Gly	Thr	Asp	Gly	Lys	Thr	Tyr	Asp	Asn
		115					120					125			

Arg	Cys	Ala	Leu	Cys	Ala	Glu	Asn	Ala	Lys	Thr	Gly	Ser	Gln	Ile	Gly
	130					135					140				

Val	Lys	Ser	Glu	Gly	Glu	Cys	Lys	Ser	Ser	Asn	Pro	Glu	Gln	Asp	Val
145					150					155					160

SUBSTITUTE SHEET (RULE 26)

74

Cys Ser Ala Phe Arg Pro Phe Val Arg Asp Gly Arg Leu Gly Cys Thr  
 165 170 175  
 Arg Glu Asn Asp Pro Val Leu Gly Pro Asp Gly Lys Thr His Gly Asn  
 180 185 190  
 Lys Cys Ala Met Cys Ala Xaa Leu Xaa Xaa Lys Glu Ala Glu Asn Ala  
 195 200 205  
 Lys Arg Glu Gly Glu Thr Arg Ile Arg Arg Asn Ala Glu Lys Asp Phe  
 210 215 220  
 Cys Lys Glu Xaa Glu Lys Gln Val Arg Asn Gly Arg Leu Phe Cys Thr  
 225 230 235 240  
 Arg Glu Ser Asp Pro Val Arg Gly Pro Asp Gly Arg Met His Gly Asn  
 245 250 255  
 Lys Cys Ala Leu Cys Ala Glu Ile Phe Lys Gln Arg Phe Ser Glu Glu  
 260 265 270  
 Asn Ser Lys Thr Asp Gln Asn Leu Gly Lys Ala Glu Glu Lys Thr Lys  
 275 280 285  
 Val Lys Arg Glu Ile Val Lys Leu Cys Ser Gln Tyr Gln Asn Gln Ala  
 290 295 300  
 Lys Asn Gly Ile Leu Phe Cys Thr Arg Glu Asn Asp Pro Ile Arg Gly  
 305 310 315 320  
 Pro Asp Gly Lys Met His Gly Asn Leu Cys Ser Met Cys Gln Ala Tyr  
 325 330 335  
 Phe Gln Ala Glu Asn Glu Glu Lys Lys Lys Ala Glu Ala Arg Ala Arg  
 340 345 350  
 Asn Lys Arg Glu Ser Gly Lys Ala Thr Ser Tyr Ala Glu Leu Cys Ser  
 355 360 365  
 Glu Tyr Arg Lys Leu Val Arg Asn Gly Lys Leu Ala Cys Thr Arg Glu  
 370 375 380  
 Asn Asn Pro Ile Gln Gly Pro Asp Gly Lys Val His Gly Asn Thr Cys  
 385 390 395 400  
 Ser Met Cys Glu Val Phe Phe Gln Ala Glu Glu Glu Glu Lys Lys Lys  
 405 410 415  
 Lys Glu Gly Xaa Ser Arg Asn Lys Arg Gln Ser Lys Ser Thr Ala Ser  
 420 425 430  
 Phe Xaa Glu Leu Cys Ser Glu Xaa Arg Lys Ser Arg Lys Asn Gly Arg  
 435 440 445  
 Leu Phe Cys Xaa Arg Glu Asn Asp Pro Ile Gln Gly Pro Asp Gly Lys  
 450 455 460

SUBSTITUTE SHEET (RULE 26)

75

Met His Gly Asn Thr Cys Ser Met Cys Glu Ala Phe Phe Gln Gln Glu  
 465 470 475 480

Glu Arg Ala Arg Ala Lys Ala Lys Arg Glu Ala Ala Lys Glu Ile Cys  
 485 490 495

Ser Glu Phe Arg Asp Gln Val Arg Asn Gly Thr Leu Ile Cys Thr Arg  
 500 505 510

Glu His Asn Pro Val Arg Gly Pro Asp Gly Lys Met His Gly Asn Lys  
 515 520 525

Cys Ala Met Cys Ala Ser Val Phe Lys Leu Glu Lys Lys Lys Lys  
 530 535 540

Lys Lys Lys Lys Lys Gly Arg Pro Leu Xaa  
 545 550

<210> 128

<211> 308

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (308)

<223> Xaa equals stop translation

<400> 128

Met Asn Thr Val Leu Leu Ser Leu Leu Phe Ser Leu Pro Arg Ile Val  
 1 5 10 15

Tyr Ala Met Ala Ala Asp Gly Leu Phe Phe Gln Val Phe Ala His Val  
 20 25 30

His Pro Arg Thr Gln Val Pro Val Ala Gly Thr Leu Ala Phe Gly Leu  
 35 40 45

Leu Thr Ala Phe Leu Ala Leu Leu Leu Asp Leu Glu Ser Leu Val Gln  
 50 55 60

Phe Leu Ser Leu Gly Thr Leu Leu Ala Tyr Thr Phe Val Ala Thr Ser  
 65 70 75 80

Ile Ile Val Leu Arg Phe Gln Lys Ser Ser Pro Pro Ser Ser Pro Gly  
 85 90 95

Pro Ala Ser Pro Gly Pro Leu Thr Lys Gln Gln Ser Ser Phe Ser Asp  
 100 105 110

His Leu Gln Leu Val Gly Thr Val His Ala Ser Val Pro Glu Pro Gly  
 115 120 125

Glu Leu Lys Pro Ala Leu Arg Pro Tyr Leu Gly Phe Leu Asp Gly Tyr  
 130 135 140

**SUBSTITUTE SHEET (RULE 26)**

76

Ser Pro Gly Ala Val Val Thr Trp Ala Leu Gly Val Met Leu Ala Ser  
 145 150 155 160

Ala Ile Thr Ile Gly Cys Val Leu Val Phe Gly Asn Ser Thr Leu His  
 165 170 175

Leu Pro His Trp Gly Tyr Ile Leu Leu Leu Leu Thr Ser Val Met  
 180 185 190

Phe Leu Leu Ser Leu Leu Val Leu Gly Ala His Gln Gln Gln Tyr Arg  
 195 200 205

Glu Asp Leu Phe Gln Ile Pro Met Val Pro Leu Ile Pro Ala Leu Ser  
 210 215 220

Ile Val Leu Asn Ile Cys Leu Met Leu Lys Leu Ser Tyr Leu Thr Trp  
 225 230 235 240

Val Arg Phe Ser Ile Trp Leu Leu Met Gly Leu Ala Val Tyr Phe Gly  
 245 250 255

Tyr Gly Ile Arg His Ser Lys Glu Asn Gln Arg Glu Leu Pro Gly Leu  
 260 265 270

Asn Ser Thr His Tyr Val Val Phe Pro Arg Gly Ser Leu Glu Glu Thr  
 275 280 285

Val Gln Ala Met Gln Pro Pro Ser Gln Ala Pro Ala Gln Asp Pro Gly  
 290 295 300

His Met Glu Xaa  
 305

<210> 129  
 <211> 167  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (167)  
 <223> Xaa equals stop translation

<400> 129  
 Met Ala Ala Ala Val Leu Ala Met Thr Leu Ala Pro Thr Val Ser Gly  
 1 5 10 15

Thr Thr Ser Lys Cys Ser Ser Arg Arg Trp Cys Pro Val Pro Ala Ser  
 20 25 30

Ser Ser Cys Val Ser His Leu Leu Gly Ser Gly Cys Ala Pro Cys Ala  
 35 40 45

Pro Trp Thr Ala His Pro Arg Gln Pro Ser Gln Cys Trp Ser Ala Arg  
 50 55 60

SUBSTITUTE SHEET (RULE 26)

77

Ala Pro Arg Arg Leu Gly Ser Arg Pro Arg Arg Tyr Leu Leu Thr Gly  
 65 70 75 80

Gln Ala Asn Gly Ser Leu Ala Met Trp Asp Leu Thr Thr Ala Met Asp  
 85 90 95

Gly Leu Gly Gln Ala Pro Ala Gly Gly Leu Thr Glu Gln Glu Leu Met  
 100 105 110

Glu Gln Leu Glu His Cys Glu Leu Ala Pro Pro Ala Pro Phe Ser Ser  
 115 120 125

Leu Met Gly Leu Ser Pro Gln Pro Leu Thr Pro His Leu Pro His Gln  
 130 135 140

Pro Pro Leu Ser Leu Gln Gln His Leu Leu Val Trp Pro Pro Trp Glu  
 145 150 155 160

Pro Lys Pro Pro Ala Gly Xaa  
 165

&lt;210&gt; 130

&lt;211&gt; 306

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (306)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 130

Met Ala Ala Gly Leu Ala Arg Leu Leu Leu Leu Gly Leu Ser Ala  
 1 5 10 15

Gly Gly Pro Ala Pro Ala Gly Ala Ala Lys Met Lys Val Val Glu Glu  
 20 25 30

Pro Asn Ala Phe Gly Val Asn Asn Pro Phe Leu Pro Gln Ala Ser Arg  
 35 40 45

Leu Gln Ala Lys Arg Asp Pro Ser Pro Val Ser Gly Pro Val His Leu  
 50 55 60

Phe Arg Leu Ser Gly Lys Cys Phe Ser Leu Val Glu Ser Thr Tyr Lys  
 65 70 75 80

Tyr Glu Phe Cys Pro Phe His Asn Val Thr Gln His Glu Gln Thr Phe  
 85 90 95

Arg Trp Asn Ala Tyr Ser Gly Ile Leu Gly Ile Trp His Glu Trp Glu  
 100 105 110

Ile Ala Asn Asn Thr Phe Thr Gly Met Trp Met Arg Asp Gly Asp Ala  
 115 120 125

SUBSTITUTE SHEET (RULE 26)

78

Cys Arg Ser Arg Ser Arg Gln Ser Lys Val Glu Leu Ala Cys Gly Lys  
 130 135 140  
 Ser Asn Arg Leu Ala His Val Ser Glu Pro Ser Thr Cys Val Tyr Ala  
 145 150 155 160  
 Leu Thr Phe Glu Thr Pro Leu Val Cys His Pro His Ala Leu Leu Val  
 165 170 175  
 Tyr Pro Thr Leu Pro Glu Ala Leu Gln Arg Gln Trp Asp Gln Val Glu  
 180 185 190  
 Gln Asp Leu Ala Asp Glu Leu Ile Thr Pro Gln Gly His Glu Lys Leu  
 195 200 205  
 Leu Arg Thr Leu Phe Glu Asp Ala Gly Tyr Leu Lys Thr Pro Glu Glu  
 210 215 220  
 Asn Glu Pro Thr Gln Leu Glu Gly Gly Pro Asp Ser Leu Gly Phe Glu  
 225 230 235 240  
 Thr Leu Glu Asn Cys Arg Lys Ala His Lys Glu Leu Ser Lys Glu Ile  
 245 250 255  
 Lys Arg Leu Lys Gly Leu Leu Thr Gln His Gly Ile Pro Tyr Thr Arg  
 260 265 270  
 Pro Thr Glu Thr Ser Asn Leu Glu His Leu Gly His Glu Thr Pro Arg  
 275 280 285  
 Ala Lys Ser Pro Glu Gln Leu Arg Gly Asp Pro Gly Leu Arg Gly Ser  
 290 295 300  
 Leu Xaa  
 305

<210> 131  
 <211> 220  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (56)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (58)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (204)  
 <223> Xaa equals any of the naturally occurring L-amino acids

SUBSTITUTE SHEET (RULE 26)



&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (209)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (220)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 131

Met Pro Cys Leu Glu Ala Val Ala Leu Ile Leu Leu Ile Leu Leu Val  
 1 5 10 15

Pro Asp Pro Pro Arg Gly Ala Ala Glu Thr Gln Gly Glu Gly Ala Val  
 20 25 30

Gly Gly Phe Arg Ser Ser Trp Cys Glu Asp Val Arg Tyr Leu Gly Lys  
 35 40 45

Asn Trp Ser Phe Val Trp Ser Xaa Leu Xaa Val Thr Ala Met Ala Phe  
 50 55 60

Val Thr Gly Ala Leu Gly Phe Trp Ala Pro Lys Phe Leu Leu Glu Ala  
 65 70 75 80

Arg Val Val His Gly Leu Gln Pro Pro Cys Phe Gln Glu Pro Cys Ser  
 85 90 95

Asn Pro Asp Ser Leu Ile Phe Gly Ala Leu Thr Ile Met Thr Gly Val  
 100 105 110

Ile Gly Val Ile Leu Gly Ala Glu Ala Ala Arg Arg Tyr Lys Lys Val  
 115 120 125

Ile Pro Gly Ala Glu Pro Leu Ile Cys Ala Ser Ser Leu Leu Ala Thr  
 130 135 140

Ala Pro Cys Leu Tyr Leu Ala Leu Val Leu Ala Pro Thr Thr Leu Leu  
 145 150 155 160

Ala Ser Tyr Val Phe Leu Gly Leu Gly Glu Leu Leu Leu Ser Cys Asn  
 165 170 175

Trp Ala Val Val Ala Asp Ile Leu Leu Ser Val Val Val Pro Arg Cys  
 180 185 190

Arg Gly Thr Ala Glu Ala Leu Gln Ile Thr Val Xaa His Ile Leu Gly  
 195 200 205

Xaa Leu Ala Ala Leu Ser His Arg Thr Tyr Leu Xaa  
 210 215 220

&lt;210&gt; 132

&lt;211&gt; 99

&lt;212&gt; PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (99)

<223> Xaa equals stop translation

<400> 132

Met Met Asn Gln His Leu Leu Glu Ser Phe Gly Ser Pro Ser Ser Leu  
1 5 10 15

Phe Ile Val Phe Ile Leu Leu Ile Trp Met Leu Gln Arg Cys Lys Asp  
20 25 30

Phe Phe Leu Cys Cys Tyr Arg Val Val Leu Thr Pro Ser Phe Trp Gln  
35 40 45

Lys His Gln His Pro Asp Pro Lys Ile Lys His His Leu Lys Leu Tyr  
50 55 60

Ser Leu Lys Tyr Ser Ser Ser Gly Gln Asn Asn Phe Arg Lys Asp Lys  
65 70 75 80

His Trp Leu Ser Gly His Thr Glu Glu Ala Asn Leu Ile Lys Glu Glu  
85 90 95

Trp Lys Xaa

<210> 133

<211> 61

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (61)

<223> Xaa equals stop translation

<400> 133

Met Thr Ser Ser Leu Phe Ile Phe Leu Phe Leu Trp Phe Cys Pro Pro  
1 5 10 15

Pro Arg Ile Ser Phe Val Leu Cys Trp Pro Gln Pro His Ser Gln Val  
20 25 30

His Ile Gln His Glu Lys Ala Asp His Leu Phe Gln Ser Leu Lys Gln  
35 40 45

Lys Ala Pro Gly Leu Leu Gln Trp Ala Arg Ile Val Xaa  
50 55 60

<210> 134

<211> 248

<212> PRT

SUBSTITUTE SHEET (RULE 26)

<213> Homo sapiens

<220>

<221> SITE

<222> (14)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (141)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (248)

<223> Xaa equals stop translation

<400> 134

Met Ala Val Pro Ala Leu Thr Pro Ala Ala Val Arg Ala Xaa Gly Leu  
1 5 10 15

Leu Gly Val Ser Trp Thr Trp Ala Leu Phe Thr Pro Leu Val Ala Leu  
20 25 30

Gly Arg Glu Gly Gly Ser Gln Asp Ser Ala Thr Thr Pro Ser Arg Pro  
35 40 45

Pro Gly Arg Pro Arg Ile Val Asp Ile Ala Thr Ile Val His Cys Tyr  
50 55 60

Ala Glu Glu Arg Gln Ser Ala Glu Asp Tyr Glu Lys Glu Glu Ser His  
65 70 75 80

Arg Gln Arg Arg Leu Lys Glu Arg Glu Arg Ile Gly Glu Leu Gly Ala  
85 90 95

Pro Glu Val Trp Gly Pro Ser Pro Lys Phe Pro Gln Leu Asp Ser Asp  
100 105 110

Glu His Thr Pro Val Glu Asp Glu Glu Glu Val Thr His Gln Lys Ser  
115 120 125

Ser Ser Ser Asp Ser Asn Ser Glu Glu His Arg Lys Xaa Lys Thr Ser  
130 135 140

Arg Ser Arg Asn Lys Lys Lys Arg Lys Asn Lys Ser Ser Lys Arg Lys  
145 150 155 160

His Arg Lys Tyr Ser Asp Ser Asp Ser Asn Ser Glu Ser Asp Thr Asn  
165 170 175

Ser Asp Ser Asp Asp Asp Lys Lys Arg Val Lys Ala Lys Lys Lys Lys  
180 185 190

Lys Lys Lys Lys His Lys Thr Lys Lys Lys Lys Asn Lys Lys Thr Lys  
195 200 205

SUBSTITUTE SHEET (RULE 26)

82

Lys Glu Ser Ser Asp Ser Ser Cys Lys Asp Ser Glu Glu Asp Leu Ser  
 210 215 220

Glu Ala Thr Trp Asp Gly Ala Ala Lys Cys Gly Arg Tyr Tyr Gly Phe  
 225 230 235 240

Asn Arg Ala Arg Ser Thr Tyr Xaa  
 245

&lt;210&gt; 135

&lt;211&gt; 41

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (41)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 135

Met Val Cys Phe Tyr Ala Leu Leu Leu Cys Phe Leu Ser Ser Val Glu  
 1 5 10 15

Ile Gly Pro Leu Ser Trp Leu Leu Cys Leu Ser His Ile Lys Cys His  
 20 25 30

Phe Thr Ala Leu Pro Phe Glu Ala Xaa  
 35 40

&lt;210&gt; 136

&lt;211&gt; 75

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (75)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 136

Met Leu His Leu Phe Cys Ser Gln Pro Leu Gly Leu Leu Phe Leu Leu  
 1 5 10 15

Ile Phe Leu Gly Leu Asp Ser Leu Pro Arg Cys Leu Thr Ala Thr Arg  
 20 25 30

Leu Gln Ser Pro Ile Ile Ile Phe Ser Thr Leu Ser Cys Ile Cys Ser  
 35 40 45

Thr Ser Trp Leu Glu Leu Cys Ser Val Tyr Phe Leu Thr Leu Asn Tyr  
 50 55 60

Leu His Val Val Pro Pro Cys Phe Leu Ile Xaa  
 65 70 75

SUBSTITUTE SHEET (RULE 26)

<210> 137  
 <211> 75  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (75)  
 <223> Xaa equals stop translation

<400> 137  
 Met Gly Val Leu Thr Arg Glu Leu Phe Gly Val Val Gly Met Leu Tyr  
           1                  5                  10                  15  
 Ile Leu Ile Val Gly Met Val Thr Trp Leu Asp Ala Phe Val Lys Thr  
                   20                  25                  30  
 His Leu Met Val Met Gln Asn Glu Tyr Ile Leu Phe Tyr Val Asn Tyr  
                   35                  40                  45  
 Thr Ser Lys Leu Asn Phe Phe Lys Lys Phe Leu Leu Lys Ser Lys Asp  
           50                  55                  60  
 Ile Cys Gly Ala Ser Cys Lys Phe Tyr Cys Xaa  
           65                  70                  75

<210> 138  
 <211> 58  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (58)  
 <223> Xaa equals stop translation

<400> 138  
 Met Lys Val Leu Leu Ser Leu Ser Leu Val Gly Leu Phe Ile Gly Phe  
           1                  5                  10                  15  
 Ser Asp Ala Val Leu Asn Glu Thr Cys Arg Phe Trp Ile Asn Thr Ser  
                   20                  25                  30  
 Ser Lys Gly Asn Leu Gln Ile Leu Lys Asn Gln Ile Gln Ile Ile Asp  
           35                  40                  45  
 Arg Leu Arg Lys Met Pro Ala Ser Ala Xaa  
           50                  55

<210> 139  
 <211> 173  
 <212> PRT  
 <213> Homo sapiens

**SUBSTITUTE SHEET (RULE 26)**

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (76)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (124)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 139

Met	Leu	Gly	Ser	Pro	Cys	Leu	Leu	Trp	Leu	Leu	Ala	Val	Thr	Phe	Leu
1				5				10						15	

Val	Pro	Arg	Ala	Gln	Pro	Leu	Ala	Pro	Gln	Asp	Phe	Glu	Glu	Glu	Glu
			20					25					30		

Ala	Asp	Glu	Thr	Glu	Thr	Ala	Trp	Pro	Pro	Leu	Pro	Ala	Val	Pro	Cys
	35						40					45			

Asp	Tyr	Asp	His	Cys	Arg	His	Leu	Gln	Val	Pro	Cys	Lys	Glu	Leu	Gln
	50						55				60				

Arg	Val	Gly	Pro	Ala	Ala	Cys	Leu	Cys	Pro	Gly	Xaa	Ser	Ser	Pro	Ala
65					70					75					80

Gln	Pro	Pro	Asp	Pro	Pro	Arg	Met	Gly	Glu	Val	Arg	Ile	Ala	Ala	Glu
			85						90					95	

Glu	Gly	Arg	Ala	Val	Val	His	Trp	Cys	Ala	Pro	Phe	Ser	Pro	Val	Leu
		100						105					110		

His	Tyr	Trp	Leu	Leu	Leu	Trp	Asp	Gly	Ser	Glu	Xaa	Arg	Arg	Arg	Gly
		115					120					125			

Pro	Pro	Leu	Asn	Ala	Thr	Val	Arg	Arg	Ala	Glu	Leu	Lys	Gly	Leu	Lys
	130					135					140				

Pro	Gly	Gly	Ile	Tyr	Val	Val	Cys	Val	Val	Ala	Ala	Asn	Glu	Ala	Gly
145					150					155					160

Ala	Ser	Arg	Val	Pro	Gln	Ala	Gly	Gly	Glu	Gly	Leu	Glu
			165						170			

&lt;210&gt; 140

&lt;211&gt; 46

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (46)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 140

Met Thr Ile His Ala Leu Leu Val Tyr Ala Cys Asn Ser Lys Cys Leu

SUBSTITUTE SHEET (RULE 26)

85  
 1 5 10 15  
 Trp Phe Ser Ile Ser His Leu His Phe Cys Leu Val Thr Leu Leu Ile  
 20 25 30  
 Leu Thr Asn Met Thr Glu Ser Ser Phe Ser Leu Lys Gly Xaa  
 35 40 45

<210> 141  
 <211> 58  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (58)  
 <223> Xaa equals stop translation

<400> 141  
 Met Val Tyr Arg Ala Phe Leu Ile Ile Ile Leu Arg Phe Ile Leu Ile  
 1 5 10 15  
 Phe Leu Phe Lys Leu Asn Tyr Ser Lys Leu Cys Pro Glu Ile Pro Phe  
 20 25 30  
 Gly Leu Lys Phe Phe Ser Phe Val Cys Ile Lys Val Gln Ile Lys Lys  
 35 40 45  
 Thr Ser Arg Lys Arg Arg Pro Tyr Leu Xaa  
 50 55

<210> 142  
 <211> 67  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (67)  
 <223> Xaa equals stop translation

<400> 142  
 Met Phe Val Glu Arg Trp Leu Pro Cys Phe Leu Val Val Ala Val Val  
 1 5 10 15  
 Val Trp Val Phe Ala Cys Gly Pro Val Glu Asp Lys Glu Asp Ser Phe  
 20 25 30  
 Gly Trp Ser Ser Tyr Phe Leu Ala Ser Gly Leu Pro Pro Leu Leu Phe  
 35 40 45  
 Glu Ala Ser Gln Thr Arg Thr Val Arg Ala Gly Arg Leu Gly Val Phe  
 50 55 60  
 Val Cys Xaa

SUBSTITUTE SHEET (RULE 26)

65

&lt;210&gt; 143

&lt;211&gt; 53

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (53)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 143

Met Ile Phe Lys Leu Leu Ile Phe Arg Ile Phe Phe His Glu Leu Ala  
 1 5 10 15

Leu Ala Leu Cys Ile Ser Asn Leu Val Ser Leu Pro Trp Leu Ser Tyr  
 20 25 30

Phe Trp Cys Pro Glu Met Gln Asn Leu Phe Leu Leu Asp Thr His Ile  
 35 40 45

Trp Val Leu Met Xaa  
 50

&lt;210&gt; 144

&lt;211&gt; 66

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (66)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 144

Met Val Leu Ser Val Ala Leu Leu His Ala Leu Ser His Leu Met Pro  
 1 5 10 15

Cys Lys Thr Cys Leu Ala Ser Thr Ser Pro Ser Ala Met Ile Val Ser  
 20 25 30

Phe Leu Arg Pro Pro Gln Pro Ala Met Trp Asn Cys Glu Ser Ile Lys  
 35 40 45

Pro Phe Leu Phe Ile His Tyr Pro Val Ser Gly Ser Ile Phe Ile Ala  
 50 55 60

Val Xaa  
 65

&lt;210&gt; 145

&lt;211&gt; 57

&lt;212&gt; PRT

SUBSTITUTE SHEET (RULE 26)



<213> Homo sapiens

<220>

<221> SITE

<222> (57)

<223> Xaa equals stop translation

<400> 145

Met Val Ala Ile Leu Leu Arg Glu Leu Pro Leu Ala Phe Leu Leu Val  
1 5 10 15

Gly Ser Ser Gly Asp Lys Phe Cys Phe Thr Ser Ser Glu Asn Val Leu  
20 25 30

Leu Ser Phe Ser Phe Leu Lys Asp Ile Phe Ala Gly Tyr Lys Asn Ser  
35 40 45

Gly Leu Met Val Leu Phe Ile Val Xaa  
50 55

<210> 146

<211> 67

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (67)

<223> Xaa equals stop translation

<400> 146

Met Ser Asn Phe Ile Ser Ile Thr Cys Leu Val Phe Thr Ile Leu Gly  
1 5 10 15

His Leu Val Ser Leu Gln Val Ala His Ser Ser Val Phe Glu Phe Lys  
20 25 30

Thr Leu Tyr Val Leu Lys Thr Asn Arg Tyr Ser Gln Ser Leu Phe Arg  
35 40 45

His Phe Cys His Leu Ser Phe Ile Arg Thr Arg Lys Ile Phe Leu Lys  
50 55 60

Asn Asn Xaa  
65

<210> 147

<211> 49

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (49)

<223> Xaa equals stop translation

**SUBSTITUTE SHEET (RULE 26)**

&lt;400&gt; 147

Met Met Lys Tyr Phe Phe Asp Val Val Val Phe Leu Thr Phe Phe Leu  
 1 5 10 15

Val Phe Ser Leu Ser Ile Phe Leu Ser Asp Glu Glu Phe Pro Val Ser  
 20 25 30

Arg Thr Gln Asn Ile Gly Leu Cys His Phe Asn Pro Ser Phe Ser Glu  
 35 40 45

Xaa

&lt;210&gt; 148

&lt;211&gt; 89

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (89)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 148

Met Leu Leu Leu Cys Leu Tyr Cys Thr Phe Phe Leu Met Pro Phe Ile  
 1 5 10 15

Ile Lys Tyr Thr Cys Phe His Leu Val Phe Gly Gln Ile Pro Val Thr  
 20 25 30

Val His Val Asn Ile Trp Gln His Lys Asn Val Thr Phe Phe Ile Leu  
 35 40 45

His Cys Gly Ile Pro Ala Leu Thr Arg Asp Ser Ala Ala Leu Thr Tyr  
 50 55 60

Ser Asn Asp Gly Thr Val Ile Glu Thr Leu Leu Phe Leu Ile Leu Tyr  
 65 70 75 80

Leu Asp Leu Asn Ile Ile Cys Cys Xaa  
 85

&lt;210&gt; 149

&lt;211&gt; 77

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (77)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 149

Met Thr Leu Tyr Ser Lys Leu Leu Trp Leu Phe Lys Gly Glu Leu Leu

89

1 5 10 15

Phe Pro Leu Val Leu Ala Tyr Val Leu Leu Leu Tyr Ile Val Thr Lys  
20 25 30

Phe Asn Tyr Leu Ile Leu Lys Leu Phe Pro Asn Lys Ile Gln Ile Lys  
35 40 45

Arg Gly Ser Ile Ala Ser Asn Arg Ser Leu Glu Ser Ser Ala Ser Leu  
50 55 60

Pro Ala Arg Lys Glu Glu Lys Leu Leu Lys Lys Phe Xaa  
65 70 75

<210> 150  
<211> 42  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (42)  
<223> Xaa equals stop translation

<400> 150

Met Asn Leu Ser Phe Leu Ser Phe Phe Leu Phe Phe Tyr Leu Leu Trp  
1 5 10 15

Ser Pro Ala Glu Ser Val Tyr Lys Lys Gly Met Val Lys Lys Asn Leu  
20 25 30

Ser His Ser Ile Val Glu Lys Ile Lys Xaa  
35 40

<210> 151  
<211> 46  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (46)  
<223> Xaa equals stop translation

<400> 151

Met Asn Ala Leu Pro Asn Leu Ala Trp Leu Pro Phe Val Pro Ala Leu  
1 5 10 15

Ala Ala Ala Ser Pro Ala Gly Leu Ala Ala Pro Glu Ser Arg Asp Val  
20 25 30

Pro Phe Pro Val Ser Pro Ala Thr Gln Leu Asn Ile Gly Xaa  
35 40 45

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<210> 152  
<211> 42  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (42)  
<223> Xaa equals stop translation

<400> 152  
Met Leu His Leu Leu Cys Leu Gly Leu His Leu Val Pro Pro Gly Leu  
1 5 10 15  
Leu Ser Val Asn Ser Leu Gln Ser Thr Gln Cys Ser Leu Phe Ser Ala  
20 25 30  
Ala Lys Phe Phe Ser Ile Val Gln Val Xaa  
35 40

<210> 153  
<211> 44  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (44)  
<223> Xaa equals stop translation

<400> 153  
Met Pro Tyr Met Phe Arg Pro Ala Phe Leu Asn Cys Gly Thr Phe Ala  
1 5 10 15  
Ile Phe Gly Gln Leu Asn Ser Val Val Gly Ala Val Leu Cys Ile Ala  
20 25 30  
Gly Cys Leu Ala Ala Ser Leu Ala Ser Thr Tyr Xaa  
35 40

<210> 154  
<211> 123  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (123)  
<223> Xaa equals stop translation

<400> 154  
Met Pro Pro Leu Ala Pro Gln Leu Cys Arg Ala Val Phe Leu Val Pro  
1 5 10 15  
Ile Leu Leu Leu Leu Gln Val Lys Pro Leu Asn Gly Ser Pro Gly Pro

91

20

25

30

Lys Asp Gly Ser Gln Thr Glu Lys Thr Pro Ser Ala Asp Gln Asn Gln  
           35                          40                          45  
 Glu Gln Phe Glu Glu His Phe Val Ala Ser Ser Val Gly Glu Met Trp  
           50                          55                          60  
 Gln Val Val Asp Met Ala Gln Gln Glu Glu Asp Gln Ser Ser Lys Thr  
           65                          70                          75                          80  
 Ala Ala Val His Lys His Ser Phe His Leu Ser Phe Cys Phe Ser Leu  
                           85                          90                          95  
 Ala Ser Val Met Val Phe Ser Gly Gly Pro Leu Arg Arg Thr Phe Pro  
                           100                          105                          110  
 Asn Ile Gln Leu Cys Phe Met Leu Thr His Xaa  
           115                          120

&lt;210&gt; 155

&lt;211&gt; 42

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (42)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 155

Met Lys Gln Phe Gly Phe Gly His Pro Ile Lys Leu Leu Lys Thr Lys  
           1                          5                          10                          15

Leu Cys Arg Ile Val Phe Tyr Leu Val Phe Phe Val Trp Pro Gln Ser  
                           20                          25                          30

Ser Val Ile Arg Glu Ala Thr Gln Thr Xaa  
           35                          40

&lt;210&gt; 156

&lt;211&gt; 56

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (56)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 156

Met Val Leu Ala Ala Pro Leu Val Ala Phe Pro Cys Ile Leu Leu Phe  
           1                          5                          10                          15

Ala Phe Ser Pro Ser Ala Val Arg Asp His Val Gly Asp Ser Arg Ser

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92

20

25

30

Asp Val Pro Ile Phe Ala Cys Leu Ala Leu Ala Ser Leu Ala Leu Gly  
 35 40 45

Ser Val Leu Leu Val Ala Phe Xaa  
 50 55

&lt;210&gt; 157

&lt;211&gt; 45

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (45)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 157

Met Met Lys Met Val Leu Gly Leu Phe Phe Leu Met Asn Leu Leu Ser  
 1 5 10 15

Gly Lys Lys Ser Val Arg His His Ser Lys Asn Tyr Val Lys Lys Met  
 20 25 30

Gln Thr Phe Gln Phe Pro Arg Val Tyr Lys Leu Met Xaa  
 35 40 45

&lt;210&gt; 158

&lt;211&gt; 86

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (86)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 158

Met Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val  
 1 5 10 15

Gly Phe Pro Val Ser Gln Asp Gln Glu Arg Glu Lys Arg Ser Ile Ser  
 20 25 30

Asp Ser Asp Glu Leu Ala Ser Gly Phe Phe Val Phe Pro Tyr Pro Tyr  
 35 40 45

Pro Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe  
 50 55 60

Arg Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro  
 65 70 75 80

Leu Pro Ser Glu Lys Xaa

SUBSTITUTE SHEET (RULE 26)

85

<210> 159  
 <211> 45  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (45)  
 <223> Xaa equals stop translation  
  
 <400> 159  
 Met Ile Cys Leu Cys Ser Ile Lys Met Leu Leu Leu Phe Cys Gln Leu  
   1                  5                  10                  15  
 Thr Phe Ala Leu Ile Thr Cys Ile Asn Leu Gln Ser Leu Tyr Leu Phe  
                   20                  25                  30  
 Ser Tyr Gln Gln Ile Ile Gly Ile His Ser His Val Xaa  
           35                  40                  45

<210> 160  
 <211> 69  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (69)  
 <223> Xaa equals stop translation  
  
 <400> 160  
 Met Trp Leu Arg Gly Ile His Pro Phe Leu Trp Leu Ser Gly Ile His  
   1                  5                  10                  15  
 Ser Phe Pro Trp Leu Ser Gly Gly Pro Ser Leu Gly Thr Ser Ser Glu  
           20                  25                  30  
 Gln Pro Thr Ser Leu Glu Asp Gly Lys Leu Ile Cys Leu Phe Thr Asp  
           35                  40                  45  
 Phe Ser Gly Ser Ser Phe Gly Leu Phe Met Arg Glu Ala Ala Lys Asn  
   50                  55                  60  
 Ile Ser Gln Met Xaa  
   65

<210> 161  
 <211> 53  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>

SUBSTITUTE SHEET (RULE 26)

&lt;221&gt; SITE

&lt;222&gt; (53)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 161

Met Leu Tyr Asp Ser Asn Leu Cys Ser Val Trp His Leu Tyr Leu Ile  
 1 5 10 15

Leu His Leu Cys Lys Thr Phe Val Tyr Cys Gly Cys Val His Ser Ser  
 20 25 30

Tyr Leu Ile Ser Gly Thr Val Asn Thr Gln Tyr Phe Ile Val Gln Thr  
 35 40 45

Val Leu Leu Phe Xaa  
 50

&lt;210&gt; 162

&lt;211&gt; 57

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (57)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 162

Met Arg Val Lys Ile Ser Tyr Leu Met Ile Ala Leu Thr Val Val Gly  
 1 5 10 15

Cys Ile Phe Met Val Ile Glu Gly Lys Lys Ala Ala Gln Arg His Glu  
 20 25 30

Thr Leu Thr Ser Leu Asn Leu Glu Lys Lys Ala Arg Leu Lys Glu Glu  
 35 40 45

Ala Ala Met Lys Ala Lys Thr Glu Xaa  
 50 55

&lt;210&gt; 163

&lt;211&gt; 56

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (56)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 163

Met Arg Glu Lys Thr Gly Ala Leu Pro Arg Cys Leu Gly Leu Leu Gly  
 1 5 10 15

Val Gly Leu Leu Trp Arg Trp Cys Gly Arg Arg Ala Arg Ala Gly Val

## SUBSTITUTE SHEET (RULE 26)



Leu Val Ser Phe Gly Arg Ala Asp Ser Ile Val Gly Asp Gly Leu Pro

```

<400> 166
Met Leu Trp Leu Leu Phe Phe Leu Val Thr Ala Ile His Ala Glu Leu
  1             5             10             15

Cys Gln Pro Gly Ala Glu Asn Ala Phe Lys Val Arg Leu Ser Ile Arg
          20             25             30

Thr Ala Leu Gly Asp Lys Ala Tyr Ala Trp Asp Thr Asn Glu Glu Tyr
      35             40             45

Leu Phe Lys Ala Met Val Ala Phe Ser Met Arg Lys Val Pro Asn Arg
      50             55             60

Glu Ala Thr Glu Ile Ser His Val Leu Leu Cys Asn Val Thr Gln Arg
  65             70             75             80

Tyr His Ser Gly Leu Trp Leu Gln Thr Leu Gln Lys Ile Thr Pro Phe
          85             90             95

Leu Leu Leu Arg Cys Asn Gln Pro Xaa
      100             105

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```
<210> 167
<211> 77
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (77)
<223> Xaa equals stop translation
```

&lt;400&gt; 167

Met Thr Lys Ala Arg Leu Phe Arg Leu Trp Leu Val Leu Gly Ser Val  
 1 5 10 15

Phe Met Ile Leu Leu Ile Ile Val Tyr Trp Asp Ser Ala Ala Pro Arg  
 20 25 30

Thr Ser Thr Cys Thr Arg Pro Ser Leu Gly Arg Thr Arg Gly Arg Arg  
 35 40 45

Cys Pro Arg Pro Gly Arg Thr Gly Gln Gly Ala His Gly Arg Leu Arg  
 50 55 60

Cys Arg Arg Val Ser Gly Gln Phe Leu Met Leu Ala Xaa  
 65 70 75

&lt;210&gt; 168

&lt;211&gt; 355

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (355)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 168

Met Trp Arg Leu Trp Pro Gly Ser Pro Leu Val Pro Leu Ser Trp Leu  
 1 5 10 15

Trp Pro Ala Arg Ala Ala Phe Leu Ser Gly Pro Trp Thr Leu Pro Pro  
 20 25 30

Cys Leu Pro Asp Pro Leu Leu Ala Val Pro Lys Cys Cys Leu Thr Leu  
 35 40 45

Gly Ile His Leu Leu Pro Ala Trp Pro Gly Pro Pro Val Gly Gly Gly  
 50 55 60

Cys Ser Gln Leu His Arg Gly Cys Cys Tyr Pro Gly Met Gly Cys Leu  
 65 70 75 80

Asn Arg Asp Leu Cys Pro Pro Ser Leu Val Ser Arg Arg Trp Gly Asp  
 85 90 95

Gln Leu Leu Trp Ser Pro Asp Gly Ser Lys Ile Leu Ala Thr Thr Pro  
 100 105 110

Ser Ala Val Phe Arg Val Trp Glu Ala Gln Met Trp Thr Cys Glu Arg  
 115 120 125

Trp Pro Thr Leu Ser Gly Arg Cys Gln Thr Gly Cys Trp Ser Pro Asp  
 130 135 140

Gly Ser Arg Leu Leu Phe Thr Val Leu Gly Glu Pro Leu Ile Tyr Ser

SUBSTITUTE SHEET (RULE 26)

98

145                      150                      155                      160  
 Leu Ser Phe Pro Glu Arg Cys Gly Glu Gly Lys Gly Cys Val Gly Gly  
                                  165                      170                      175  
 Ala Lys Ser Ala Thr Ile Val Ala Asp Leu Ser Glu Thr Thr Ile Gln  
                                  180                      185                      190  
 Thr Pro Asp Gly Glu Glu Arg Leu Gly Gly Glu Ala His Ser Met Val  
                                  195                      200                      205  
 Trp Asp Pro Ser Gly Glu Arg Leu Ala Val Leu Met Lys Gly Lys Pro  
                                  210                      215                      220  
 Arg Val Gln Asp Gly Lys Pro Val Ile Leu Leu Phe Arg Thr Arg Asn  
 225                                   230                      235                      240  
 Ser Pro Val Phe Glu Leu Leu Pro Cys Gly Ile Ile Gln Gly Glu Pro  
                                  245                      250                      255  
 Gly Ala Gln Pro Gln Leu Ile Thr Phe His Leu Pro Ser Thr Lys Gly  
                                  260                      265                      270  
 Pro Cys Ser Val Trp Ala Gly Pro Gln Ala Glu Leu Pro Thr Ser Arg  
                                  275                      280                      285  
 Cys Thr Leu Ser Met Pro Ser Phe His Val Leu Ala Gln Cys Leu Gly  
                                  290                      295                      300  
 Gly Pro Arg Asn Pro Leu Leu Gly Val Glu Ala Leu Phe Met Thr Cys  
 305                                   310                      315                      320  
 Pro Ser Leu Leu Arg His Pro Gln Pro Leu Pro Leu Gly Thr Leu Ser  
                                  325                      330                      335  
 Gln Gly His His Leu Phe Cys Pro Thr Pro His Ile Pro Thr Ser Lys  
                                  340                      345                      350  
 Asn Lys Xaa  
                                  355

&lt;210&gt; 169

&lt;211&gt; 90

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (90)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 169

Met Cys Val Cys Tyr Phe Leu Val Phe Leu Gln Ile Trp Ala Arg Leu  
 1                      5                      10                      15

Ser His Leu Leu Val Trp Ile Tyr Pro Gly Ala Gly Leu Gln Pro Gly

SUBSTITUTE SHEET (RULE 26)

99

20

25

30

Lys Gly His Pro Ala Gln Ser Leu Phe Pro His Glu His Cys His Leu  
                   35                  40                  45

Met Pro Gln His Ser Leu Thr Leu Lys Ile Leu Glu Glu Lys Leu Gly  
           50                  55                  60

Gly Lys Gly Glu Ser Gly Ser Asn Phe Thr Phe Leu His Cys Lys Ile  
   65                  70                  75                  80

Leu Ala Thr Ser Ala Leu Asn Phe Ser Xaa  
                   85                  90

&lt;210&gt; 170

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (59)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 170

Met Val Leu Pro Phe Val Leu Leu Phe Arg Pro Asn Phe Ile Ser Val  
   1                  5                  10                  15

Leu His Pro Leu Phe Tyr Ser His Cys Leu Phe Leu Tyr Leu Ile Ser  
           20                  25                  30

Pro Val His Ser Ser Ser Ile Ile Tyr Tyr Lys Pro Asp His Cys His  
           35                  40                  45

Tyr Thr Pro Phe Ile Pro Gly Leu Leu Gln Xaa  
   50                  55

&lt;210&gt; 171

&lt;211&gt; 70

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (70)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 171

Met Leu Leu Ser Lys Glu His Thr Ser Leu Gly Trp Leu Val Ile Phe  
   1                  5                  10                  15

Leu Thr Leu Ala Ser Gln Leu Ile Ser Tyr Gly Ser Arg Thr Gly Asn  
           20                  25                  30

Ser Arg Cys Pro Pro Cys Leu Tyr Arg Thr Leu His Thr Val Ser Thr

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100

35

40

45

Ser His Val Leu Ser Ser Leu Phe Val Ser Thr Phe Ser Gly Asp Glu  
 50 55 60

Leu Val Trp Thr Thr Xaa  
 65 70

&lt;210&gt; 172

&lt;211&gt; 79

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (79)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 172

Met Val Leu Asp Phe Lys Arg Ala Gly Ser Phe Phe Leu Ser Phe Leu  
 1 5 10 15

Trp Thr Arg Glu Ala Phe Ala Phe Ile Phe Thr Leu Pro Leu Leu Leu  
 20 25 30

Ser Leu Cys Arg Gly Lys Met Lys Asn Ser Pro Arg Ser Asp Leu Ser  
 35 40 45

Arg Leu Lys Lys Asn Val Phe Asn Ala Phe Leu Pro Cys Leu Val Pro  
 50 55 60

Arg Phe Ile Ser Asn Arg Gly Cys Pro Val Tyr Arg Ser Cys Xaa  
 65 70 75

&lt;210&gt; 173

&lt;211&gt; 174

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (150)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (152)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (174)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 173

SUBSTITUTE SHEET (RULE 26)

101

Met Gly Val Pro Thr Ala Pro Glu Ala Gly Ser Trp Arg Trp Gly Ser  
 1 5 10 15

Leu Leu Phe Ala Leu Phe Leu Ala Ala Ser Leu Asp Ile Thr Ala Ala  
 20 25 30

Ala Leu Ala Thr Gly Ala Cys Ile Val Glu Ser Ser Ala Ser Pro Ser  
 35 40 45

Ser Cys Ser Trp Ser Thr Ser Lys Gly Arg Gln Pro Pro Thr Ala Val  
 50 55 60

Pro Arg Ser Trp Cys Gly Trp Thr Ala Thr Phe Lys Gly Leu Lys Thr  
 65 70 75 80

Pro Ala Leu Lys Pro His His Leu Pro Arg Gly Tyr Pro Arg Pro Lys  
 85 90 95

Ser Gly Thr Pro Cys Pro Met Trp Pro Ser Gly Ser Leu Leu Ser Leu  
 100 105 110

Gly Gly Ile Cys Phe Arg Ser Pro Ala Pro Pro Cys Leu Leu Gln Ala  
 115 120 125

Pro Glu Thr Ser Ser Ser His Pro Trp Thr Leu Ser Leu Thr Leu Gln  
 130 135 140

Thr Leu Arg Ser Ser Xaa Pro Xaa Gly Gly Gln Trp Ala Val Val Ala  
 145 150 155 160

Gly Ser Gly Ala Gly Ala Phe Glu Pro Gly Leu Ala Leu Xaa  
 165 170

&lt;210&gt; 174

&lt;211&gt; 64

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (64)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 174

Met Phe Val Leu Trp Val Phe Lys Ile Thr Tyr Ile Tyr Ile Leu Phe  
 1 5 10 15

Ala Lys Asn Lys Ser Leu Ala Ser Cys Gln Met Ile Ala Lys Val Asp  
 20 25 30

Leu Thr Phe Phe Val Ile Met Tyr Ile Phe Ile His Thr Pro Asn Thr  
 35 40 45

Leu Ser Asp Phe Cys Tyr Phe Leu Gly Ser Thr Ala Leu Arg Leu Xaa  
 50 55 60

SUBSTITUTE SHEET (RULE 26)

<210> 175  
 <211> 43  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (43)  
 <223> Xaa equals stop translation

<400> 175  
 Met Ile Ser Ala Gln Ser Ser Ile Ser Trp Ala Leu Ile Phe Ile Met  
           1                  5                  10                  15  
 Ala Pro Ala Leu His Leu Val Leu Arg Phe Pro Ser Lys Phe Lys Pro  
                   20                  25                  30  
 Glu Arg Lys Gly Glu Ala Arg Ser Pro Lys Xaa  
           35                  40

<210> 176  
 <211> 114  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (114)  
 <223> Xaa equals stop translation

<400> 176  
 Met Trp Ile Ala Gly Pro Ser Trp Val Pro Leu Arg Tyr Val Val Trp  
           1                  5                  10                  15  
 Leu Met His Leu Glu Arg Ile Cys Ala Leu His Asn Cys Arg Gly Asn  
                   20                  25                  30  
 Met Leu Ser Trp Pro Leu Gln Ile Arg Val Ala Val Leu Gly Cys Cys  
           35                  40                  45  
 Thr Lys Thr Pro Ala Val Gly Phe Leu Gln Val Ala Gly Ser Pro His  
           50                  55                  60  
 Ser Cys Gln Asp Pro Gly Pro Cys Ser His Ser Ala Ala Ile Phe Pro  
           65                  70                  75                  80  
 Pro Cys Glu Arg Gly Leu Cys Gly Asp Gly Pro Arg Cys Val Arg Gly  
                   85                  90                  95  
 Cys Val His Cys His Arg Ser Leu Leu His Glu Pro Ala Trp Thr Gln  
           100                  105                  110

SUBSTITUTE SHEET (RULE 26)



Gly Xaa

<210> 177  
 <211> 156  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (156)  
 <223> Xaa equals stop translation

<400> 177  
 Met Ala Ser Ser Leu Ala Phe Leu Leu Leu Asn Phe His Val Ser Leu  
           1                  5                  10                  15  
 Leu Leu Val Gln Leu Leu Thr Pro Cys Ser Ala Gln Phe Ser Val Leu  
                   20                  25                  30  
 Gly Pro Ser Gly Pro Ile Leu Ala Met Val Gly Glu Asp Ala Asp Leu  
           35                  40                  45  
 Pro Cys His Leu Phe Pro Thr Met Ser Ala Glu Thr Met Glu Leu Lys  
           50                  55                  60  
 Trp Val Ser Ser Ser Leu Arg Gln Val Val Asn Val Tyr Ala Asp Gly  
           65                  70                  75                  80  
 Lys Glu Val Glu Asp Arg Gln Ser Ala Pro Tyr Arg Gly Arg Thr Ser  
                   85                  90                  95  
 Ile Leu Arg Asp Gly Ile Thr Ala Gly Lys Ala Ala Leu Arg Ile His  
           100                  105                  110  
 Asn Val Thr Ala Ser Asp Ser Gly Lys Tyr Leu Cys Tyr Phe Gln Asp  
           115                  120                  125  
 Gly Asp Phe Tyr Glu Lys Ala Leu Val Glu Leu Lys Val Ala Ala Leu  
           130                  135                  140  
 Gly Ser Asn Leu His Val Gly Ser Glu Gly Leu Xaa  
           145                  150                  155

<210> 178  
 <211> 89  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (89)  
 <223> Xaa equals stop translation

<400> 178

SUBSTITUTE SHEET (RULE 26)

104

Met Trp Pro Ser Gln Val Pro Leu Leu Ala Phe Cys Phe Leu Leu Val  
 1 5 10 15  
 Lys Ser Thr Ser Asn Ile Asn Leu Pro Thr Pro Pro Pro Ser Ser Leu  
 20 25 30  
 Glu Asn Ser Ser Phe Val Val Ser Gln Arg Gly Asn Leu Ile Val Phe  
 35 40 45  
 Gly Gly Gln Lys Lys Ala Thr Phe Arg Tyr His Phe Tyr Leu Asp Arg  
 50 55 60  
 Met Pro Phe Tyr Ser Gln Ile Ser Val Tyr Phe Val Asn Gly Phe Arg  
 65 70 75 80  
 Val Asn Gly Tyr Leu Cys Asn Asn Xaa  
 85

&lt;210&gt; 179

&lt;211&gt; 197

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (197)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 179

Met Ala Phe Arg Tyr Leu Ser Trp Ile Leu Phe Pro Leu Leu Gly Cys  
 1 5 10 15  
 Tyr Ala Val Tyr Ser Leu Leu Tyr Leu Glu His Lys Gly Trp Tyr Ser  
 20 25 30  
 Trp Val Leu Ser Met Leu Tyr Gly Phe Leu Leu Thr Phe Gly Phe Ile  
 35 40 45  
 Thr Met Thr Pro Gln Leu Phe Ile Asn Tyr Lys Leu Lys Ser Val Ala  
 50 55 60  
 His Leu Pro Trp Arg Met Leu Thr Tyr Lys Ala Leu Asn Thr Phe Ile  
 65 70 75 80  
 Asp Asp Leu Phe Ala Phe Val Ile Lys Met Pro Val Met Tyr Arg Ile  
 85 90 95  
 Gly Cys Leu Arg Asp Asp Val Val Phe Phe Ile Tyr Leu Tyr Gln Arg  
 100 105 110  
 Trp Ile Tyr Arg Val Asp Pro Thr Arg Val Asn Glu Phe Gly Met Ser  
 115 120 125  
 Gly Glu Asp Pro Thr Ala Ala Ala Pro Val Ala Glu Val Pro Thr Ala  
 130 135 140

SUBSTITUTE SHEET (RULE 26)

105

Ala Gly Ala Leu Thr Pro Thr Pro Ala Pro Thr Thr Thr Thr Ala Thr  
 145 150 155 160

Arg Glu Glu Ala Ser Thr Ser Leu Pro Thr Lys Pro Thr Gln Gly Ala  
 165 170 175

Ser Ser Ala Ser Glu Pro Gln Glu Ala Pro Pro Lys Pro Ala Glu Asp  
 180 185 190

Lys Lys Lys Asp Xaa  
 195

&lt;210&gt; 180

&lt;211&gt; 129

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (129)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 180

Met Tyr Glu Cys Phe Leu Ser Leu Ser Leu Leu Lys Ser Cys Lys Ala  
 1 5 10 15

Val Ser Gly Leu Met Cys Leu Leu Leu Pro Arg Leu Gly Leu Leu Leu  
 20 25 30

Leu Leu Pro Ser Glu Arg Cys Phe Cys Trp Ile Pro Val Tyr Ser Leu  
 35 40 45

Ile Thr Cys Leu Ala Glu Cys Ser Val Val Leu Arg Asp Pro Gly Phe  
 50 55 60

Ala Gly Ala Phe Gln Val His Arg Arg Gln Ala Cys Phe Ser Thr Leu  
 65 70 75 80

Arg Trp Ser Cys Leu Leu Leu Trp Trp Val Ser Arg Val Ser Ala Gly  
 85 90 95

Arg Pro Leu Ile Gly Ser Pro His Met Met Ala Pro Ser Thr Phe Cys  
 100 105 110

Pro Thr Val Arg Gly Pro Gly Thr Cys Ala Ser Ser Asp Pro Asp Gly  
 115 120 125

Xaa

&lt;210&gt; 181

&lt;211&gt; 155

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (155)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 181

Met	Pro	Ala	Glu	Lys	Arg	Ile	Phe	Gly	Ala	Val	Leu	Leu	Phe	Ser	Trp
1				5					10					15	

Thr	Val	Tyr	Leu	Trp	Glu	Thr	Phe	Leu	Ala	Gln	Arg	Gln	Arg	Arg	Ile
			20					25					30		

Tyr	Lys	Thr	Thr	Thr	His	Val	Pro	Pro	Glu	Leu	Gly	Gln	Ile	Met	Asp
		35					40					45			

Ser	Glu	Thr	Phe	Glu	Lys	Ser	Arg	Leu	Tyr	Gln	Leu	Asp	Lys	Ser	Thr
	50					55					60				

Phe	Ser	Phe	Trp	Ser	Gly	Leu	Tyr	Ser	Glu	Thr	Glu	Gly	Thr	Leu	Asn
65					70					75					80

Leu	Leu	Phe	Gly	Gly	Ile	Pro	Tyr	Leu	Trp	Arg	Leu	Ser	Gly	Arg	Phe
				85					90					95	

Cys	Gly	Tyr	Ala	Gly	Phe	Gly	Pro	Glu	Tyr	Glu	Ile	Thr	Gln	Ser	Leu
			100					105					110		

Val	Phe	Leu	Leu	Leu	Ala	Thr	Leu	Phe	Ser	Ala	Leu	Thr	Gly	Val	Pro
		115					120						125		

Trp	Ser	Leu	Tyr	Asn	Thr	Phe	Val	Ile	Lys	Lys	Thr	Trp	Leu	Gln	Ser
	130					135					140				

Thr	Asp	Phe	Gly	Val	Leu	His	Met	Glu	Ile	Xaa
145					150					155

&lt;210&gt; 182

&lt;211&gt; 107

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (107)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 182

Met	Ser	Leu	Ser	Trp	Met	Val	His	Leu	Leu	Gly	Leu	Pro	Asn	Gly	Thr
1				5						10				15	

Val	Trp	Tyr	Leu	Pro	Phe	Val	Cys	Phe	Thr	Arg	Gly	Ser	Pro	Met	Gly
			20					25					30		

Gly	Gly	Ser	Gly	Gln	Trp	Arg	Trp	Asp	Arg	Lys	Phe	Ser	Lys	Thr	Leu
		35					40					45			

SUBSTITUTE SHEET (RULE 26)

107

Leu Gly Asn Leu Phe Val Ala Phe Lys Glu Met Cys Gly Glu Asp Ile  
 50 55 60

Trp Met Leu Ala Ala Ile Leu Glu Leu Arg Thr Gln Glu Trp Trp Lys  
 65 70 75 80

Gly Arg Arg Asn Arg Val Phe Val Ala Val Val Lys Leu Leu Lys Phe  
 85 90 95

Pro Ser Cys Gln Ala Ser Cys Tyr Met Arg Xaa  
 100 105

<210> 183  
 <211> 48  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (48)  
 <223> Xaa equals stop translation

<400> 183  
 Met Ile Asn Glu Trp Cys Phe Lys Leu Leu Ser Leu Trp Ser Phe Ala  
 1 5 10 15

Tyr Ser Asn Cys Lys Leu Ile His Lys Cys Lys Phe Val Phe Leu Lys  
 20 25 30

Lys Lys Lys Thr Gly Lys Glu Val Ser Val Lys Gly Ser Lys Leu Xaa  
 35 40 45

<210> 184  
 <211> 127  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (127)  
 <223> Xaa equals stop translation

<400> 184  
 Met Trp Leu Gly Ser Trp Leu Thr Ser Leu Leu Leu Ser Pro Tyr Gly  
 1 5 10 15

Ser Gly Trp Glu Lys Val Pro Cys Cys Val Thr Gly His Leu Arg Ser  
 20 25 30

Cys Ser Cys Cys Leu Leu Gly Leu Ala Gly Val Gln Ser Asp His Phe  
 35 40 45

SUBSTITUTE SHEET (RULE 26)

108

Ser Glu Gly Phe Phe Ser Glu Tyr Ser Ser Asp Val Leu Pro Trp Gly  
 50 55 60

Arg Arg Ser Phe Leu Pro Gln Gly Asp Ala Ser Leu Leu Ala Cys Glu  
 65 70 75 80

Cys Phe Leu His Leu Gln Val Val Trp Gly Gln Phe Cys Leu Leu Glu  
 85 90 95

Ala Trp Ala Gly Phe Thr Glu Gly Ser Met Pro Ala Pro Ser Cys Arg  
 100 105 110

Val His Phe Trp Cys Arg Val Asn Thr Cys Pro Phe Met Ser Xaa  
 115 120 125

&lt;210&gt; 185

&lt;211&gt; 87

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (87)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 185

Met Leu Cys Gly Tyr Val Ile Asn Asn Ile Trp Leu Ile Phe Thr Tyr  
 1 5 10 15

Phe Ile Cys Ile Tyr Ile Ser Arg Ser Tyr Ile Tyr Ile Thr Gln Glu  
 20 25 30

Thr Gln Val Ile Tyr Ile Cys Gln Glu Met Tyr Asp Tyr Phe Gly Glu  
 35 40 45

Asn Gly Pro Lys Cys Glu Lys Asp Ile Lys Lys Thr Lys Lys Thr Lys  
 50 55 60

Lys Lys His Tyr Phe Pro Leu Arg Asn Ile Leu Tyr Ile Ser Lys Glu  
 65 70 75 80

Glu Lys Leu Lys Asp Ile Xaa  
 85

&lt;210&gt; 186

&lt;211&gt; 58

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (58)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 186

SUBSTITUTE SHEET (RULE 26)

109

Met Ile Val Ser Tyr Arg Ile Val Ser Leu Pro Ser Ser Val Leu Cys  
 1 5 10 15

Leu Phe Ile Pro Pro Phe Leu Leu Ile Phe Tyr Cys Leu His Ser Phe  
 20 25 30

Val Phe Ser Gln Met Leu Tyr Ser Trp Asn Tyr His Val Thr Phe Gln  
 35 40 45

Met Ala Phe Ser Leu Ile Ile Cys Val Xaa  
 50 55

&lt;210&gt; 187

&lt;211&gt; 69

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (69)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 187

Met Val Ala Ser Gln Ala Trp Trp Leu Ser Asn Leu Trp His Leu Trp  
 1 5 10 15

Glu Val Gly Ser Ala Gln Gly Leu Pro Leu Asp Pro Pro Ala Leu Ala  
 20 25 30

Pro Tyr Leu Pro Trp Ala Leu Arg Trp Pro Cys Phe Ser Gly Phe Ala  
 35 40 45

Ser Leu Ala Gly Ala Leu Val Leu Ala His Ser Leu Pro Thr Ala Trp  
 50 55 60

Pro Gly Ser Ser Xaa  
 65

&lt;210&gt; 188

&lt;211&gt; 48

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (48)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 188

Met Tyr Leu Phe Leu Leu Cys Cys Phe Ile Ser Glu His Cys Ala Gln  
 1 5 10 15

His Ser Phe Pro His Thr Cys Pro Asn Trp Lys Thr Arg Val Leu Ser  
 20 25 30

SUBSTITUTE SHEET (RULE 26)

110

Phe Pro Leu His Pro Cys Pro His Leu Ile His Pro Asn Asn Thr Xaa  
                   35                                  40                                  45

<210> 189  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (5)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (51)  
 <223> Xaa equals stop translation

<400> 189  
 Met Leu Ser Ser Xaa Tyr Val Pro Met Cys Gln His Phe Ile Tyr Pro  
       1                                  5                                  10                                  15

Val Leu Trp Val Leu Val His Phe Phe Ser Phe Ile Gln Ile Gln Lys  
                   20                                  25                                  30

Asn Thr Asp Gly Ser Asn Val Lys Leu Thr Arg Asn Pro Gly Thr Phe  
                   35                                  40                                  45

Ile Ser Xaa  
           50

<210> 190  
 <211> 56  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (56)  
 <223> Xaa equals stop translation

<400> 190  
 Met Ala Val Arg Val Leu Trp Gly Gly Leu Ser Leu Leu Arg Val Leu  
       1                                  5                                  10                                  15

Trp Cys Leu Leu Pro Gln Thr Gly Tyr Val His Pro Asp Glu Phe Phe  
                   20                                  25                                  30

Gln Ser Pro Glu Val Met Ala Gly Lys Thr Pro His Val Trp Leu Arg  
                   35                                  40                                  45

Gln Ala Ala Ala Glu Ser Ala Xaa

SUBSTITUTE SHEET (RULE 26)



111

50

55

<210> 191  
 <211> 127  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (127)  
 <223> Xaa equals stop translation

<400> 191  
 Met Cys Ser Ser Phe Pro Arg Met Ala Leu Cys Ala Leu Trp Met Trp  
   1                  5                  10                  15  
 Pro Ser Val Lys Ser Ser Val Pro Leu Pro Leu Arg Glu Pro Phe Leu  
                   20                  25                  30  
 Trp Arg Ser Pro Gly Ser Gln Cys Leu Leu Cys Leu Gln Thr Ile His  
           35                  40                  45  
 Val Ser Cys Ser Glu Ala Cys Pro Leu Leu Glu Asn Ile Ser Lys Asn  
   50                  55                  60  
 Cys Thr Ile Pro Gln Arg Asp Leu Asp Asn Met Ala Phe Pro Gln Ala  
   65                  70                  75                  80  
 Leu Pro Leu Glu Lys Arg Cys Glu Arg Phe Leu Gln Lys Ser Tyr Arg  
                   85                  90                  95  
 Lys Leu Glu Lys Asn Pro Glu Lys Glu Glu Glu His Trp Ala Arg Leu  
                   100                  105                  110  
 Gln Arg Tyr Ser Leu Ser Leu Gln Arg Glu Asn Phe Lys Lys Xaa  
   115                  120                  125

<210> 192  
 <211> 70  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (70)  
 <223> Xaa equals stop translation

<400> 192  
 Met Pro Phe Gln Leu Pro Leu Gln Leu Leu Leu Arg Leu Ile Cys  
   1                  5                  10                  15  
 Glu Phe Phe Leu Ala Pro Ala Leu Asn Cys Asn Leu Thr Gly Thr Val  
                   20                  25                  30  
 Ile Phe Phe Thr Leu Met Ile Ser Leu Gln Leu Met Ile Phe Phe Thr

SUBSTITUTE SHEET (RULE 26)

112

35

40

45

Leu Gln Phe Ala Asp Gly Phe Gln Ile Gly Val Asp Leu Gln Leu Ser  
 50 55 60

Glu Leu Asn Ile Leu Xaa  
 65 70

&lt;210&gt; 193

&lt;211&gt; 71

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (71)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 193

Met Ile Ser Gly Val Leu Ile Phe Asn Leu Ile Ala Ser Ser Trp Val  
 1 5 10 15

Leu Cys Phe Pro Leu Cys Asp Leu Ser Cys Gln Lys Thr Leu Arg Ile  
 20 25 30

Phe Phe Ala Ser Phe Phe His Ala Val Cys Val His Val Ser Cys Thr  
 35 40 45

Ser Trp Gln Pro Leu Val Leu Phe Ile Lys Trp Trp Val Val Gly Cys  
 50 55 60

Ser Pro Ala Val Ser Leu Xaa  
 65 70

&lt;210&gt; 194

&lt;211&gt; 130

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (130)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 194

Met His Val Leu Pro Leu Leu Leu Ser Leu Leu Leu Leu Leu Leu  
 1 5 10 15

Leu Ser Ala Ser Phe Val Thr Phe Ser Thr Pro Thr Ser Ser Arg Asn  
 20 25 30

Ser Ser Cys Pro Asp Cys Glu Ser Leu Asn Thr Gly Leu Pro Ser Leu  
 35 40 45

Met Met Phe Gly Gly Ser Leu Leu Lys Trp Val Gln Asn Thr His Gly

SUBSTITUTE SHEET (RULE 26)

```

<400> 196
Met Ala Ala Phe Phe Ala Leu Ala Ala Leu Val Gln Val Val Tyr Thr
  1             5             10             15

Ile Pro Ala Val Leu Thr Leu Leu Val Gly Leu Asn Pro Glu Val Thr

```

114

20                      25                      30

Gly Asn Val Ile Trp Lys Ser Ile Ser Ala Ile His Ile Leu Phe Cys  
           35                      40                      45

Thr Val Trp Ala Val Gly Leu Ala Ser Tyr Leu Leu His Arg Thr Gln  
           50                      55                      60

Gln Asn Ile Leu His Glu Glu Glu Gly Arg Ser Cys Leu Val Trp Xaa  
           65                      70                      75                      80

<210> 197  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (42)  
 <223> Xaa equals stop translation

<400> 197  
 Met Lys His Met Asn Thr Leu Pro Ile Phe Ser Ser Leu Ile Ser Phe  
       1                      5                      10                      15

Leu Pro Ala Val Ser Ala Gly Arg Ser Ala Ile Thr Thr Leu Cys Asn  
           20                      25                      30

Ile Thr Glu Gln Leu Glu Val Leu Gly Xaa  
           35                      40

<210> 198  
 <211> 197  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (197)  
 <223> Xaa equals stop translation

<400> 198  
 Met Lys Tyr Leu Arg His Arg Arg Pro Asn Ala Thr Leu Ile Leu Ala  
       1                      5                      10                      15

Ile Gly Ala Phe Thr Leu Leu Leu Phe Ser Leu Leu Val Ser Pro Pro  
           20                      25                      30

Thr Cys Lys Val Gln Glu Gln Pro Pro Ala Ile Pro Glu Ala Leu Ala  
           35                      40                      45

Trp Pro Thr Pro Pro Thr Arg Pro Ala Pro Ala Pro Cys His Ala Asn

**SUBSTITUTE SHEET (RULE 26)**

115

50	55	60
Thr Ser Met Val Thr His Pro Asp Phe Ala Thr Gln Pro Gln His Val		
65	70	75 80
Gln Asn Phe Leu Leu Tyr Arg His Cys Arg His Phe Pro Leu Leu Gln		
	85	90 95
Asp Val Pro Pro Ser Lys Cys Ala Gln Pro Val Phe Leu Leu Leu Val		
	100	105 110
Ile Lys Ser Ser Pro Ser Asn Tyr Val Arg Arg Glu Leu Leu Arg Arg		
	115	120 125
Thr Trp Gly Arg Glu Arg Lys Val Arg Gly Leu Gln Leu Arg Leu Leu		
	130	135 140
Phe Leu Val Gly Thr Ala Ser Asn Pro His Glu Ala Arg Lys Val Asn		
145	150	155 160
Arg Leu Leu Glu Leu Glu Ala Gln Thr His Gly Asp Ile Leu Gln Trp		
	165	170 175
Asp Phe His Asp Ser Phe Phe Asn Leu Thr Leu Lys Gln Val Arg Trp		
	180	185 190
Thr Gly Val Thr Xaa		
	195	

&lt;210&gt; 199

&lt;211&gt; 124

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (124)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 199

Met Lys Leu Leu Leu Leu Ala Leu Pro Met Leu Val Leu Leu Pro Gln
1 5 10 15

Val Ile Pro Ala Tyr Ser Gly Glu Lys Lys Cys Trp Asn Arg Ser Gly
20 25 30

His Cys Arg Lys Gln Cys Lys Asp Gly Glu Ala Val Lys Asp Thr Cys
35 40 45

Lys Asn Leu Arg Ala Cys Cys Ile Pro Ser Asn Glu Asp His Arg Arg
50 55 60

Val Pro Ala Thr Ser Pro Thr Pro Leu Ser Asp Ser Thr Pro Gly Ile
65 70 75 80

Ile Asp Asp Ile Leu Thr Val Arg Phe Thr Thr Asp Tyr Phe Glu Val

SUBSTITUTE SHEET (RULE 26)

Asp Leu Arg Gly Asn Ser Phe Asn Cys Asp Cys Lys Leu Lys Trp Leu  
165 170 175

NSDOCID: <WO\_\_993117A1\_I\_>

Val	Glu	Trp	Leu	Gly	His	Thr	Asn	Ala	Thr	Val	Glu	Asp	Ile	Tyr	Cys	180	185	190	
Glu	Gly	Pro	Pro	Glu	Tyr	Lys	Lys	Arg	Lys	Ile	Asn	Ser	Leu	Ser	Ser	195	200	205	
Lys	Asp	Phe	Asp	Cys	Ile	Ile	Thr	Glu	Phe	Ala	Lys	Ser	Gln	Asp	Leu	210	215	220	
Pro	Tyr	Gln	Ser	Leu	Ser	Ile	Asp	Thr	Phe	Ser	Tyr	Leu	Asn	Asp	Glu	225	230	235	240
Tyr	Val	Val	Ile	Ala	Gln	Pro	Phe	Thr	Gly	Lys	Cys	Ile	Phe	Leu	Glu	245	250	255	
Trp	Asp	His	Val	Glu	Lys	Thr	Phe	Arg	Asn	Tyr	Asp	Asn	Ile	Thr	Gly	260	265	270	
Thr	Ser	Thr	Val	Val	Cys	Lys	Pro	Ile	Val	Ile	Glu	Thr	Gln	Leu	Tyr	275	280	285	
Val	Ile	Val	Ala	Gln	Leu	Phe	Gly	Gly	Ser	His	Ile	Tyr	Lys	Arg	Asp	290	295	300	
Ser	Phe	Ala	Asn	Lys	Phe	Ile	Lys	Ile	Gln	Asp	Ile	Glu	Ile	Leu	Lys	305	310	315	320
Ile	Arg	Lys	Pro	Asn	Asp	Ile	Glu	Thr	Phe	Lys	Ile	Glu	Asn	Asn	Trp	325	330	335	
Tyr	Phe	Val	Val	Ala	Asp	Ser	Ser	Lys	Ala	Gly	Phe	Thr	Thr	Ile	Tyr	340	345	350	
Lys	Trp	Asn	Gly	Asn	Gly	Phe	Tyr	Ser	His	Gln	Ser	Leu	His	Ala	Trp	355	360	365	
Tyr	Arg	Asp	Thr	Asp	Val	Glu	Tyr	Leu	Glu	Ile	Val	Arg	Thr	Pro	Gln	370	375	380	
Thr	Leu	Arg	Thr	Pro	His	Leu	Ile	Leu	Ser	Ser	Ser	Ser	Xaa	Arg	Pro	385	390	395	400
Val	Ile	Tyr	Gln	Trp	Asn	Lys	Ala	Thr	Gln	Leu	Phe	Thr	Asn	Gln	Thr	405	410	415	
Asp	Ile	Pro	Asn	Met	Glu	Asp	Val	Tyr	Ala	Val	Lys	His	Phe	Ser	Val	420	425	430	
Lys	Gly	Asp	Val	Tyr	Ile	Cys	Leu	Thr	Arg	Phe	Ile	Gly	Asp	Ser	Lys	435	440	445	
Val	Met	Lys	Trp	Gly	Gly	Ser	Ser	Phe	Gln	Asp	Ile	Gln	Arg	Met	Pro	450	455	460	
Ser	Arg	Gly	Ser	Met	Val	Phe	Gln	Pro	Leu	Gln	Ile	Asn	Asn	Tyr	Gln	465	470	475	480

SUBSTITUTE SHEET (RULE 26)

Tyr Ala Ile Leu Gly Ser Asp Tyr Ser Phe Thr Gln Val Tyr Asn Trp  
                             485                            490                            495

Asp Ala Glu Lys Ala Lys Phe Val Lys Phe Gln Glu Leu Asn Val Gln  
                             500                            505                            510

Ala Pro Arg Ser Phe Thr His Val Ser Ile Asn Lys Arg Asn Phe Leu  
                             515                            520                            525

Phe Ala Ser Ser Phe Lys Gly Asn Thr Gln Ile Tyr Lys His Val Ile  
                             530                            535                            540

Val Asp Leu Ser Ala  
 545

<210> 201

<211> 488

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (344)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (416)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (429)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (430)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 201

Met Ile Leu Ser Leu Leu Phe Ser Leu Gly Gly Pro Leu Gly Trp Gly  
       1                            5                            10                            15

Leu Leu Gly Ala Trp Ala Gln Ala Ser Ser Thr Ser Leu Ser Asp Leu  
                             20                            25                            30

Gln Ser Ser Arg Thr Pro Gly Val Trp Lys Ala Glu Ala Glu Asp Thr  
                             35                            40                            45

Ser Lys Asp Pro Val Gly Arg Asn Trp Cys Pro Tyr Pro Met Ser Lys  
                             50                            55                            60

Leu Val Thr Leu Leu Ala Leu Cys Lys Thr Glu Lys Phe Leu Ile His  
       65                            70                            75                            80

# SUBSTITUTE SHEET (RULE 26)



Ser	Gln	Gln	Pro	Cys	Pro	Gln	Gly	Ala	Pro	Asp	Cys	Gln	Lys	Val	Lys	85	90	95	
Val	Met	Tyr	Arg	Met	Ala	His	Lys	Pro	Val	Tyr	Gln	Val	Lys	Gln	Lys	100	105	110	
Val	Leu	Thr	Ser	Leu	Ala	Trp	Arg	Cys	Cys	Pro	Gly	Tyr	Thr	Gly	Pro	115	120	125	
Asn	Cys	Glu	His	His	Asp	Ser	Met	Ala	Ile	Pro	Glu	Pro	Ala	Asp	Pro	130	135	140	
Gly	Asp	Ser	His	Gln	Glu	Pro	Gln	Asp	Gly	Pro	Val	Ser	Phe	Lys	Pro	145	150	155	160
Gly	His	Leu	Ala	Ala	Val	Ile	Asn	Glu	Val	Glu	Val	Gln	Gln	Glu	Gln	165	170	175	
Gln	Glu	His	Leu	Leu	Gly	Asp	Leu	Gln	Asn	Asp	Val	His	Arg	Val	Ala	180	185	190	
Asp	Ser	Leu	Pro	Gly	Leu	Trp	Lys	Ala	Leu	Pro	Gly	Asn	Leu	Thr	Ala	195	200	205	
Ala	Val	Met	Glu	Ala	Asn	Gln	Thr	Gly	His	Glu	Phe	Pro	Asp	Arg	Ser	210	215	220	
Leu	Glu	Gln	Val	Leu	Leu	Pro	His	Val	Asp	Thr	Phe	Leu	Gln	Val	His	225	230	235	240
Phe	Ser	Pro	Ile	Trp	Arg	Ser	Phe	Asn	Gln	Ser	Leu	His	Ser	Leu	Thr	245	250	255	
Gln	Ala	Ile	Arg	Asn	Leu	Ser	Leu	Asp	Val	Glu	Ala	Asn	Arg	Gln	Ala	260	265	270	
Ile	Ser	Arg	Val	Gln	Asp	Ser	Ala	Val	Ala	Arg	Ala	Asp	Phe	Gln	Glu	275	280	285	
Leu	Gly	Ala	Lys	Phe	Glu	Ala	Lys	Val	Gln	Glu	Asn	Thr	Gln	Arg	Val	290	295	300	
Gly	Gln	Leu	Arg	Gln	Asp	Val	Glu	Glu	Arg	Leu	His	Ala	Gln	His	Phe	305	310	315	320
Thr	Leu	His	Arg	Ser	Ile	Ser	Glu	Leu	Gln	Ala	Asp	Val	Asp	Thr	Lys	325	330	335	
Leu	Lys	Arg	Leu	His	Lys	Ala	Xaa	Glu	Ala	Pro	Gly	Thr	Asn	Gly	Ser	340	345	350	
Leu	Val	Leu	Ala	Thr	Pro	Gly	Ala	Gly	Ala	Arg	Pro	Glu	Pro	Asp	Ser	355	360	365	
Leu	Gln	Ala	Arg	Leu	Gly	Gln	Leu	Gln	Arg	Asn	Leu	Ser	Glu	Leu	His	370	375	380	

SUBSTITUTE SHEET (RULE 26)

120

Met Thr Thr Ala Arg Arg Glu Glu Glu Leu Gln Tyr Thr Leu Glu Asp  
385 390 395 400

Met Arg Ala Thr Leu Thr Arg His Val Asp Glu Ile Lys Glu Leu Xaa  
405 410 415

Ser Glu Ser Asp Glu Thr Phe Asp Gln Ile Ser Lys Xaa Xaa Arg Gln  
420 425 430

Val Glu Glu Leu Gln Val Asn His Thr Ala Leu Arg Glu Leu Arg Val  
435 440 445

Ile Leu Met Glu Lys Ser Leu Ile Met Glu Glu Asn Lys Glu Glu Val  
450 455 460

Glu Arg Gln Leu Leu Glu Leu Asn Leu Thr Leu Gln His Leu Gln Gly  
465 470 475 480

Gly Met Pro Thr Ser Ser Ser Thr  
485

<210> 202

<211> 86

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (86)

<223> Xaa equals stop translation

<400> 202

Met Ala His Gly Pro Gln Ser Leu Trp Ser Leu Gly Phe Thr Val Thr  
1 5 10 15

Leu Thr Phe Glu Leu Pro Val Gly Cys Val Leu Gly Arg Ile Cys His  
20 25 30

Pro Ile Gln Ala Cys Asn Thr Gly Leu Met Thr Pro Thr Pro Gln Gly  
35 40 45

Pro Cys Arg Thr Glu Met Met Ser Asn Asp Lys Pro Trp Leu Pro Ala  
50 55 60

Asn Ala Pro Ala His Ile Ser Leu Pro Gly Ala Arg Leu Thr Ser Thr  
65 70 75 80

Cys Ala Pro Gly Leu Xaa  
85

<210> 203

<211> 400

<212> PRT

<213> Homo sapiens

**SUBSTITUTE SHEET (RULE 26)**

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (400)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 203

Met Ala Ile His Lys Ala Leu Val Met Cys Leu Gly Leu Pro Leu Phe  
 1 5 10 15

Leu Phe Pro Gly Ala Trp Ala Gln Gly His Val Pro Pro Gly Cys Ser  
 20 25 30

Gln Gly Leu Asn Pro Leu Tyr Tyr Asn Leu Cys Asp Arg Ser Gly Ala  
 35 40 45

Trp Gly Ile Val Leu Glu Ala Val Ala Gly Ala Gly Ile Val Thr Thr  
 50 55 60

Phe Val Leu Thr Ile Ile Leu Val Ala Ser Leu Pro Phe Val Gln Asp  
 65 70 75 80

Thr Lys Lys Arg Ser Leu Leu Gly Thr Gln Val Phe Phe Leu Leu Gly  
 85 90 95

Thr Leu Gly Leu Phe Cys Leu Val Phe Ala Cys Val Val Lys Pro Asp  
 100 105 110

Phe Ser Thr Cys Ala Ser Arg Arg Phe Leu Phe Gly Val Leu Phe Ala  
 115 120 125

Ile Cys Phe Ser Cys Leu Ala Ala His Val Phe Ala Leu Asn Phe Leu  
 130 135 140

Ala Arg Lys Asn His Gly Pro Arg Gly Trp Val Ile Phe Thr Val Ala  
 145 150 155 160

Leu Leu Leu Thr Leu Val Glu Val Ile Ile Asn Thr Glu Trp Leu Ile  
 165 170 175

Ile Thr Leu Val Arg Gly Ser Gly Glu Gly Gly Pro Gln Gly Asn Ser  
 180 185 190

Ser Ala Gly Trp Ala Val Ala Ser Pro Cys Ala Ile Ala Asn Met Asp  
 195 200 205

Phe Val Met Ala Leu Ile Tyr Val Met Leu Leu Leu Leu Gly Ala Phe  
 210 215 220

Leu Gly Ala Trp Pro Ala Leu Cys Gly Arg Tyr Lys Arg Trp Arg Lys  
 225 230 235 240

His Gly Val Phe Val Leu Leu Thr Thr Ala Thr Ser Val Ala Ile Trp  
 245 250 255

Val Val Trp Ile Val Met Tyr Thr Tyr Gly Asn Lys Gln His Asn Ser  
 260 265 270

SUBSTITUTE SHEET (RULE 26)

Pro Thr Trp Asp Asp Pro Thr Leu Ala Ile Ala Leu Ala Ala Asn Ala  
 275 280 285

Trp Ala Phe Val Leu Phe Tyr Val Ile Pro Glu Val Ser Gln Val Thr  
 290 295 300

Lys Ser Ser Pro Glu Gln Ser Tyr Gln Gly Asp Met Tyr Pro Thr Arg  
 305 310 315 320

Gly Val Gly Tyr Glu Thr Ile Leu Lys Glu Gln Lys Gly Gln Ser Met  
 325 330 335

Phe Val Glu Asn Lys Ala Phe Ser Met Asp Glu Pro Val Ala Ala Lys  
 340 345 350

Arg Pro Val Ser Pro Tyr Ser Gly Tyr Asn Gly Gln Leu Leu Thr Ser  
 355 360 365

Val Tyr Gln Pro Thr Glu Met Ala Leu Met His Lys Val Pro Ser Glu  
 370 375 380

Glu Leu Thr Thr Ser Ser Ser His Gly Pro Pro Pro Thr Ala Arg Xaa  
 385 390 395 400

&lt;210&gt; 204

&lt;211&gt; 195

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (195)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 204

Met Ser Thr Ala Phe Cys Pro Ile His Ser Ser Leu Gly Ser Met Val  
 1 5 10 15

Met Cys Leu Cys Ile Leu Ser Pro Leu Cys Ile Ala Ser Lys Ser Leu  
 20 25 30

Arg Val Cys Thr Lys Ser Tyr Met Glu Gly His Gly Lys Thr Arg Val  
 35 40 45

Pro Val Val Leu Val Gly Asn Lys Ala Asp Leu Ser Pro Glu Arg Glu  
 50 55 60

Val Gln Ala Val Glu Gly Lys Lys Leu Ala Glu Ser Trp Gly Ala Thr  
 65 70 75 80

Phe Met Glu Ser Ser Ala Arg Glu Asn Gln Leu Thr Gln Gly Ile Phe  
 85 90 95

SUBSTITUTE SHEET (RULE 26)

123

Thr Lys Val Ile Gln Glu Ile Ala Arg Val Gly Glu Phe Leu Trp Ala  
 100 105 110  
 Arg Ala Ser Leu Pro Ser His Val Ser Pro Trp Val Trp Gly Asn Cys  
 115 120 125  
 Leu Ala Ser Ala Pro Gly Thr Cys His Val Pro Val Gly Gly Arg Ser  
 130 135 140  
 Ser Gly Leu His Gly Tyr Gly Cys Gln Leu Cys Ser Trp Pro Leu Asp  
 145 150 155 160  
 Thr Gln Cys Gly Ile Leu Met Phe Ala His Phe Pro Gln Ala Pro Val  
 165 170 175  
 Ala Trp Met Ser Met Phe Thr Lys Gly Gln Gly Pro Leu Met Asp Thr  
 180 185 190  
 Gly Leu Xaa  
 195

<210> 205  
 <211> 57  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (57)  
 <223> Xaa equals stop translation

<400> 205  
 Met Pro Leu Glu Glu Ser Phe Glu Ile Val Leu Lys Leu Val Pro Leu  
 1 5 10 15  
 Leu Gly Leu Glu Leu Phe Phe Phe Leu Phe Ile Ile Asn Gly Tyr Ile  
 20 25 30  
 Asn Val Tyr Cys Pro Ser Gln Tyr Phe Ile Tyr Ala Lys Asp Ser Leu  
 35 40 45  
 Ala Gly Leu Ala Leu Ile Pro Gln Xaa  
 50 55

<210> 206  
 <211> 73  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (73)  
 <223> Xaa equals stop translation

SUBSTITUTE SHEET (RULE 26)

124

&lt;400&gt; 206

Met Ile Val Ile Tyr Leu Thr Leu Thr Trp Thr Phe Leu Ile Asn Leu  
 1 5 10 15

Leu Ala Cys Pro Leu Tyr His Leu Pro Gln Met Gln Lys Lys Ala Lys  
 20 25 30

Pro Glu Thr Lys Lys Ala Lys Pro Glu Thr Lys Glu Thr Ile Gln Arg  
 35 40 45

Gln Arg Asn Leu Phe Leu Val Leu Leu Lys Gln Leu Ala Gly Lys Lys  
 50 55 60

Cys Ser Ala Leu Phe Leu Ile Val Xaa  
 65 70

&lt;210&gt; 207

&lt;211&gt; 85

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (85)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 207

Met Val Trp Cys Gln Cys Leu Cys Pro Leu Cys Ala Cys Trp Glu Glu  
 1 5 10 15

Ala Gln Ala Leu Trp Trp Pro Pro Leu Cys Thr Trp Pro Gly Glu Ala  
 20 25 30

Arg Gly Ser Gly Ala Ser Leu Arg Leu Arg Pro Pro Leu Gln Asn Lys  
 35 40 45

Leu Ser Pro Gly Val Cys Leu Ser Leu Phe Leu Ser Pro Glu Arg Asn  
 50 55 60

Ala Gly Val Pro Glu Ala Ser Leu Gln Thr Lys His Pro Cys Thr Ser  
 65 70 75 80

Tyr Gly Ser Gly Xaa  
 85

&lt;210&gt; 208

&lt;211&gt; 195

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (195)

&lt;223&gt; Xaa equals stop translation

SUBSTITUTE SHEET (RULE 26)

125

&lt;400&gt; 208

Met Trp Val Ser Leu Tyr Phe Gly Ile Leu Gly Leu Cys Ser Val Ile  
 1 5 10 15

Thr Gly Gly Cys Ile Ile Phe Leu His Trp Arg Lys Asn Leu Arg Arg  
 20 25 30

Glu Glu His Ala Gln Gln Trp Val Glu Val Met Arg Ala Ala Thr Phe  
 35 40 45

Thr Tyr Ser Pro Leu Leu Tyr Trp Ile Asn Lys Arg Arg Arg Tyr Gly  
 50 55 60

Met Asn Ala Ala Ile Asn Thr Gly Pro Ala Pro Ala Val Thr Lys Thr  
 65 70 75 80

Glu Thr Glu Val Gln Asn Pro Asp Val Leu Trp Asp Leu Asp Ile Pro  
 85 90 95

Glu Gly Arg Ser His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala  
 100 105 110

Pro Ala Pro Leu Gln Pro Ala Leu Gln Leu Ala Pro Gln Gln Pro Gln  
 115 120 125

Ala Arg Ser Pro Phe Pro Leu Pro Ile Phe Gln Glu Val Pro Phe Ala  
 130 135 140

Pro Pro Leu Cys Asn Leu Pro Pro Leu Leu Asn His Ser Val Ser Tyr  
 145 150 155 160

Pro Leu Ala Thr Cys Pro Glu Arg Asn Val Leu Phe His Ser Leu Leu  
 165 170 175

Asn Leu Ala Gln Glu Asp His Ser Phe Asn Ala Lys Pro Phe Pro Ser  
 180 185 190

Glu Leu Xaa  
 195

&lt;210&gt; 209

&lt;211&gt; 42

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (42)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 209

Met Leu Gln Arg Gly Gln His Leu Tyr Leu Val Val Phe Leu Met Val  
 1 5 10 15

Ser Phe Ile Pro Leu Leu Asn Pro Lys Gln Asp Leu Lys Lys Leu Lys  
 20 25 30

SUBSTITUTE SHEET (RULE 26)

Lys Asn Arg Thr Val Arg Asn His Phe Xaa  
 35 40

<210> 210  
 <211> 282  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (282)  
 <223> Xaa equals stop translation

<400> 210  
 Met Ser Ile Leu Thr Met Ile Ser Ser Trp Pro Phe Ser Arg Val Val  
 1 5 10 15  
 Arg Phe Trp Phe Leu His Gln Met Val Leu Asp Leu Cys Leu Gly Gln  
 20 25 30  
 Gly Val Pro Gln Gln Asn Leu Gly Lys Pro Lys Gly Lys Lys Lys Leu  
 35 40 45  
 Ser Ser Val Arg Gln Lys Phe Asp His Arg Phe Gln Pro Gln Asn Pro  
 50 55 60  
 Leu Ser Gly Ala Gln Gln Phe Val Ala Lys Asp Pro Gln Asp Asp Asp  
 65 70 75 80  
 Asp Leu Lys Leu Cys Ser His Thr Met Met Leu Pro Thr Arg Gly Gln  
 85 90 95  
 Leu Glu Gly Arg Met Ile Val Thr Ala Tyr Glu His Gly Leu Asp Asn  
 100 105 110  
 Val Thr Glu Glu Ala Val Ser Ala Val Val Tyr Ala Val Glu Asn His  
 115 120 125  
 Leu Lys Asp Ile Leu Thr Ser Val Val Ser Arg Arg Lys Ala Tyr Arg  
 130 135 140  
 Leu Arg Asp Gly His Phe Lys Tyr Ala Phe Gly Ser Asn Val Thr Pro  
 145 150 155 160  
 Gln Pro Tyr Leu Lys Asn Ser Val Val Ala Tyr Asn Asn Leu Ile Glu  
 165 170 175  
 Ser Pro Pro Ala Phe Thr Ala Pro Cys Ala Gly Gln Asn Pro Ala Ser  
 180 185 190  
 His Pro Pro Pro Asp Asp Ala Glu Gln Gln Ala Ala Leu Leu Ala  
 195 200 205  
 Cys Ser Gly Asp Thr Leu Pro Ala Ser Leu Pro Pro Val Asn Met Tyr  
 210 215 220

SUBSTITUTE SHEET (RULE 26)



127

Asp Leu Phe Glu Ala Leu Gln Val His Arg Glu Val Ile Pro Thr His  
 225                                      230                                      235                                      240  
 Thr Val Tyr Ala Leu Asn Ile Glu Arg Ile Ile Thr Lys Leu Trp His  
    245                                      250                                      255  
 Pro Asn His Glu Glu Leu Gln Gln Asp Lys Val His Arg Gln Arg Leu  
    260                                      265                                      270  
 Ala Ala Lys Glu Gly Leu Leu Leu Cys Xaa  
    275                                      280

<210> 211  
 <211> 48  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (48)  
 <223> Xaa equals stop translation

<400> 211  
 Met Pro Lys Thr Cys Leu Pro Ile Leu Cys Leu Pro Leu Thr Gln Ala  
   1  5  10  15  
 Val Val Leu Ala Gln Leu Asn Asn Phe Ser Ser Leu Asn Ile Phe Ile  
   20  25  30  
 Phe Lys Ile Lys Asn Lys Met Tyr Tyr Ile Trp Ile Tyr Asp Lys Xaa  
   35  40  45

<210> 212  
 <211> 59  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (59)  
 <223> Xaa equals stop translation

<400> 212  
 Met Trp Pro Cys Cys Leu Asp Ser Leu Leu Phe Gly Phe Trp Leu Trp  
   1  5  10  15  
 Ala Gln Gly Ile Thr Leu Leu Ser Glu Asp Ser Ile Arg Ile Val Cys  
   20  25  30  
 Ser Ser Cys Glu Pro Glu Val Leu His Val Pro Thr Pro Val Tyr Arg  
   35  40  45

SUBSTITUTE SHEET (RULE 26)

Pro Cys Pro Ser His Ser Pro Leu Thr Phe Xaa  
 50 55

<210> 213  
 <211> 43  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (43)  
 <223> Xaa equals stop translation

<400> 213  
 Met Ala Leu Gln Ser Ile Pro Ser Phe Thr Leu Leu Ile Ser Phe Phe  
 1 5 10 15

Leu Ser Thr Gln Cys Leu Arg Cys Val Tyr Asn Tyr Glu Cys Ile Leu  
 20 25 30

Phe Met Ala Phe Asn Cys Arg Met Val Phe Xaa  
 35 40

<210> 214  
 <211> 53  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (53)  
 <223> Xaa equals stop translation

<400> 214  
 Met Pro Ala Val Ser Ala Phe Phe Ser Leu Ala Ala Leu Ala Glu Val  
 1 5 10 15

Ala Ala Met Glu Asn Val His Arg Gly Gln Arg Ser Thr Pro Leu Thr  
 20 25 30

His Asp Gly Gln Pro Lys Glu Met Pro Gln Ala Pro Val Leu Ile Ser  
 35 40 45

Cys Ala Asp Gln Xaa  
 50

<210> 215  
 <211> 68  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE

SUBSTITUTE SHEET (RULE 26)

&lt;222&gt; (68)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 215

Met Cys Thr Gln Ile Leu Val Phe Met Leu Leu Ile Lys Cys Ile Phe  
 1 5 10 15

Ser Ile Asn Thr His Pro Ile Met Pro Tyr Leu Tyr Met Lys Asn Lys  
 20 25 30

Val Thr Met Leu Tyr Cys Tyr Val Leu Lys Phe Lys Ser Leu Phe Glu  
 35 40 45

Lys Pro Ser Asn Trp Cys Phe His Tyr Ile Met Ile His Leu Asp Lys  
 50 55 60

Thr Pro Asn Xaa  
 65

&lt;210&gt; 216

&lt;211&gt; 57

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (57)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 216

Met Leu Phe Val Ser Leu Leu Val Met Trp Asn Leu Phe Leu Ser Ser  
 1 5 10 15

Asp Phe Leu Phe Leu Trp Ser Val Leu Gly Tyr Tyr Met Lys Val Arg  
 20 25 30

Leu Pro Gln Ser Pro Arg Glu Ala His Cys Val Leu Leu Ile Asp Leu  
 35 40 45

Lys Met Ile Glu Ser Leu Gly Gly Xaa  
 50 55

&lt;210&gt; 217

&lt;211&gt; 56

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (56)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 217

Met Glu Gln Leu Leu Ala Ala Val Val Phe Phe Ser Ile Phe Phe Leu  
 1 5 10 15

SUBSTITUTE SHEET (RULE 26)

130

Asn Leu Leu Ala Leu Lys Met Asn Lys Val Tyr Arg Cys Ile Cys Leu  
                   20                  25                  30

Leu Phe Ser Lys Asn Met His Thr Asn Val Cys Phe Tyr Lys Ser Asn  
                   35                  40                  45

Thr His Val Ile Ile Cys Met Xaa  
           50                  55

<210> 218  
 <211> 58  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (58)  
 <223> Xaa equals stop translation

<400> 218  
 Met Cys Trp Lys Pro Lys Cys Ile Leu Leu Leu Ser Phe Val Phe Gln  
   1                  5                  10                  15

Cys Val Ala Ser Ser Thr Phe Asp Pro Leu Gly Ser Glu Arg Pro Trp  
                   20                  25                  30

Ser Gln Pro Gln Cys Pro Ile Ser Phe Pro Leu Leu Ile Thr Gly Cys  
                   35                  40                  45

Cys Trp Phe Ser Met Ser Arg Val Ser Xaa  
           50                  55

<210> 219  
 <211> 59  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (59)  
 <223> Xaa equals stop translation

<400> 219  
 Met Arg Thr Phe Leu Thr Phe Val Ile Leu Lys Val Ile Leu Ile Phe  
   1                  5                  10                  15

Leu Ser Ser Cys Ala Ser Phe Thr Arg Asn Leu Leu Thr Trp Pro Asn  
                   20                  25                  30

Asp Val Ser Thr Glu Gln Phe Glu Thr Arg Pro Phe Gly Ser Glu Leu  
                   35                  40                  45

Leu Gln Thr Val Ile Asn Val Ser Arg Thr Xaa  
           50                  55

SUBSTITUTE SHEET (RULE 26)

<210> 220  
 <211> 45  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (45)  
 <223> Xaa equals stop translation

<400> 220  
 Met Arg Phe Phe Phe Gln Ala Tyr Ser Gln Ile Cys Val Gln Asn Phe  
           1                          5                          10                          15  
 Leu Thr Phe Leu Leu Cys Ile Ile Ile Glu Phe Ile Ala Ala Asp Phe  
                           20                          25                          30  
 Tyr Asn Asp Ser Cys Cys His Val Ser Leu Asn Asn Xaa  
                           35                          40                          45

<210> 221  
 <211> 45  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (41)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (45)  
 <223> Xaa equals stop translation

<400> 221  
 Met Ile Leu Phe Asp Leu Thr Phe Phe Leu Phe Ala Pro Arg Ile Leu  
           1                          5                          10                          15  
 Ala Ser Gly Ala Cys Ser Cys Ser Ile Tyr Pro Lys Ile Thr Leu Pro  
                           20                          25                          30  
 Thr Lys Tyr Phe Ala Phe Ile Ile Xaa Thr Ser Phe Xaa  
                           35                          40                          45

<210> 222  
 <211> 52  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (52)

**SUBSTITUTE SHEET (RULE 26)**

132

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 222

Met Asp Gly Leu Ile Met Cys Leu Ile Ile Phe Gln Ile Val Asn Phe  
 1 5 10 15

Trp Leu Pro Cys Ile Ile Leu Leu Gly Ile Leu Asn Pro Thr Tyr Lys  
 20 25 30

Asn Tyr Val Met Val Ser Thr Lys Cys Trp Met Lys Arg Thr Tyr Glu  
 35 40 45

His Met Ser Xaa  
 50

&lt;210&gt; 223

&lt;211&gt; 73

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (73)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 223

Met Thr Phe Leu Phe Phe Phe Leu Phe Ser Arg Ile Leu Cys Ile Lys  
 1 5 10 15

Asn Leu Asp Leu Leu Thr Trp Lys Arg Ser Asn Pro Val Ile Ala Lys  
 20 25 30

His Leu Tyr Cys Arg Gly His Ile Thr Lys Lys Ser Lys Gly Pro Ala  
 35 40 45

Gln Trp Thr Ile Tyr Phe Ser Asp Val Gln Tyr Lys Ile Ser Leu Pro  
 50 55 60

Leu Lys Thr Leu Glu Ser Pro Phe Xaa  
 65 70

&lt;210&gt; 224

&lt;211&gt; 71

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (71)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 224

Met Leu Phe Trp Lys Phe Gly Ser Phe Leu Phe Phe Cys Leu Pro Leu  
 1 5 10 15

SUBSTITUTE SHEET (RULE 26)

133

Thr Leu Phe Cys Ile Leu Asn Glu Arg Gly Ile Met His Leu Glu Gly  
                   20                  25                  30

Gly Thr Leu Leu Asn Ser Leu Ser His Val Arg His Tyr Leu Arg Leu  
                   35                  40                  45

Arg Leu Ser Cys Phe Glu Lys Ile Pro Leu His Arg Ser Ile Phe Ile  
           50                  55                  60

Phe Leu Leu Leu Leu Leu Xaa  
   65                  70

<210> 225  
 <211> 58  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (58)  
 <223> Xaa equals stop translation

<400> 225  
 Met Ala Gly Cys Cys Leu Lys Leu Phe Gly Val Leu Ser Leu Cys Phe  
   1                  5                  10                  15

Leu Cys Gly Leu Ile Ser Ile Glu Arg Val Ile Cys Asn Pro Val Ser  
           20                  25                  30

Ala Asp Phe Gln Val Ser Thr Phe Cys Gln Arg His Cys Leu Leu Arg  
           35                  40                  45

Ser Lys Val Met Phe Pro Ile Arg Gly Xaa  
   50                  55

<210> 226  
 <211> 59  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (59)  
 <223> Xaa equals stop translation

<400> 226  
 Met Arg Ile Ser Arg Cys Asn Ile Ser Leu Glu Ile Val Ser Pro Ser  
   1                  5                  10                  15

Ile Leu Leu Thr Phe Leu Asp Leu Ile Ile Leu Leu Trp Ala Leu Ala  
           20                  25                  30

Ser Cys Tyr Arg Arg Phe Thr Ser Phe Pro Ala Leu Asn Leu Pro Asp  
           35                  40                  45

SUBSTITUTE SHEET (RULE 26)

134

Val Asn Ser Thr Leu His Tyr Leu Gln Gln Xaa  
 50 55

<210> 227  
 <211> 43  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (43)  
 <223> Xaa equals stop translation

<400> 227  
 Met Val Ala Pro Leu His Leu Phe Ile Pro Phe Ser Trp Leu Val Arg  
 1 5 10 15

Thr Ile Gly Gln Leu Leu Ser Pro Val Gly Lys Ala Leu Ser His Arg  
 20 25 30

Ser Asn Gln Met Met Pro Arg Ser Trp Gly Xaa  
 35 40

<210> 228  
 <211> 41  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (41)  
 <223> Xaa equals stop translation

<400> 228  
 Met Arg Thr Ser Leu Phe Phe Phe Phe Phe Lys Asn Ile Leu Val Leu  
 1 5 10 15

Cys Gly Thr Leu Leu Ile Ser Arg Ser Ser His Ser Gln Ser Ala Pro  
 20 25 30

Arg Gly Cys Trp Trp Pro His Lys Xaa  
 35 40

<210> 229  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (42)  
 <223> Xaa equals stop translation

<400> 229

**SUBSTITUTE SHEET (RULE 26)**



135

Met Leu Trp Lys Tyr Phe Leu Ser Leu Phe Leu Pro Trp Tyr Leu Tyr  
 1 5 10 15

Cys Phe Phe Asn Asn Asn Ile Met Phe Tyr Ser Leu His Ser Val Pro  
 20 25 30

Met Phe Ile Gln Pro Phe Leu Leu Trp Xaa  
 35 40

&lt;210&gt; 230

&lt;211&gt; 165

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (165)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 230

Met Ser Thr Arg Arg Leu Gly Val Ala Val Ala Val Leu Gly Gly Phe  
 1 5 10 15

Leu Tyr Ala Val Gly Gly Ser Asp Gly Thr Ser Pro Leu Asn Thr Val  
 20 25 30

Glu Arg Tyr Asn Pro Gln Glu Asn Arg Trp His Thr Ile Ala Pro Met  
 35 40 45

Gly Thr Arg Arg Lys His Leu Gly Cys Ala Val Tyr Gln Asp Met Ile  
 50 55 60

Tyr Ala Val Gly Gly Arg Asp Asp Thr Thr Glu Leu Ser Ser Ala Glu  
 65 70 75 80

Arg Tyr Asn Pro Arg Thr Asn Gln Trp Ser Pro Val Val Ala Met Thr  
 85 90 95

Ser Arg Arg Ser Gly Val Gly Leu Ala Val Val Asn Gly Gln Leu Met  
 100 105 110

Ala Val Gly Gly Phe Asp Gly Thr Thr Tyr Leu Lys Thr Ile Glu Val  
 115 120 125

Phe Asp Pro Asp Ala Asn Thr Trp Arg Leu Tyr Gly Gly Met Asn Tyr  
 130 135 140

Arg Arg Leu Gly Gly Gly Val Gly Val Ile Lys Met Thr His Cys Glu  
 145 150 155 160

Ser His Ile Trp Xaa  
 165

&lt;210&gt; 231

&lt;211&gt; 52

SUBSTITUTE SHEET (RULE 26)

136

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (52)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 231

Met Ala Cys Leu Ile Arg Phe Pro Ala Ile Gly Ser Leu Pro Tyr Ser  
 1 5 10 15

Thr Trp Pro Phe Phe Phe Phe Ile Phe Leu Phe Phe Ser Cys Leu Thr  
 20 25 30

Phe Ile Pro Phe Ser Pro Leu Ser Ser Phe Cys Glu Pro Tyr Pro Arg  
 35 40 45

Lys Glu Pro Xaa  
 50

&lt;210&gt; 232

&lt;211&gt; 130

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (130)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 232

Met Phe Leu Leu Asn Phe Arg Tyr Ile Met Arg Phe Phe Phe Trp Pro  
 1 5 10 15

Met Leu Gln Ala Lys Leu Met Ser Phe His Phe Leu Lys Pro Ile Ile  
 20 25 30

Phe Met Asn Ser Leu Ile Leu Cys Leu Lys Gln Ser Cys Ser Cys Glu  
 35 40 45

Val Glu Ile Ser Leu Leu Pro Leu Ser Gln Gln Thr His Arg Thr Asp  
 50 55 60

Leu Gly Phe Ser His Ser Gly Ser Gln Asn Glu Pro Phe Leu Asn Leu  
 65 70 75 80

Asp Lys Arg Ala Ala Glu Ala His Cys Ala Val Met Val Leu Cys Leu  
 85 90 95

Leu Gly Arg Asp Leu Lys Ala Arg Arg Ser Arg Glu Gly Pro Ala Leu  
 100 105 110

Cys Ser Ser Gln Val Val Ile Cys Ile Leu Lys Leu Ala Arg Lys Arg  
 115 120 125

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Phe Xaa  
130

<210> 233  
<211> 55  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (55)  
<223> Xaa equals stop translation

<400> 233  
Met Glu Phe Lys Leu Val Arg Lys Ile Gln Ile Ala Ile Leu Ile Phe  
1 5 10 15  
Tyr Leu Tyr Leu Val Ala Val Ala Phe Lys Asn Lys Phe Ser Tyr Lys  
20 25 30  
Ser Phe Gln Phe Phe Gly Leu Glu Ser Ile Phe Gln Asn Lys Lys Leu  
35 40 45  
Lys Lys Glu Tyr Leu Met Xaa  
50 55

<210> 234  
<211> 363  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (307)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (363)  
<223> Xaa equals stop translation

<400> 234  
Met Arg Thr Leu Phe Asn Leu Leu Trp Leu Ala Leu Ala Cys Ser Pro  
1 5 10 15  
Val His Thr Thr Leu Ser Lys Ser Asp Ala Lys Lys Ala Ala Ser Lys  
20 25 30  
Thr Leu Leu Glu Lys Ser Gln Phe Ser Asp Lys Pro Val Gln Asp Arg  
35 40 45  
Gly Leu Val Val Thr Asp Leu Lys Ala Glu Ser Val Val Leu Glu His  
50 55 60  
Arg Ser Tyr Cys Ser Ala Lys Ala Arg Asp Arg His Phe Ala Gly Asp

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138

65		70		75		80									
Val	Leu	Gly	Tyr	Val	Thr	Pro	Trp	Asn	Ser	His	Gly	Tyr	Asp	Val	Thr
				85					90					95	
Lys	Val	Phe	Gly	Ser	Lys	Phe	Thr	Gln	Ile	Ser	Pro	Val	Trp	Leu	Gln
			100					105					110		
Leu	Lys	Arg	Arg	Gly	Arg	Glu	Met	Phe	Glu	Val	Thr	Gly	Leu	His	Asp
		115					120					125			
Val	Asp	Gln	Gly	Trp	Met	Arg	Ala	Val	Arg	Lys	His	Ala	Lys	Gly	Leu
	130						135				140				
His	Ile	Val	Pro	Arg	Leu	Leu	Phe	Glu	Asp	Trp	Thr	Tyr	Asp	Asp	Phe
145					150					155					160
Arg	Asn	Val	Leu	Asp	Ser	Glu	Asp	Glu	Ile	Glu	Glu	Leu	Ser	Lys	Thr
				165					170					175	
Val	Val	Gln	Val	Ala	Lys	Asn	Gln	His	Phe	Asp	Gly	Phe	Val	Val	Glu
		180						185					190		
Val	Trp	Asn	Gln	Leu	Leu	Ser	Gln	Lys	Arg	Val	Thr	Asp	Gln	Leu	Gly
		195					200					205			
Met	Phe	Thr	His	Lys	Glu	Phe	Glu	Gln	Leu	Ala	Pro	Val	Leu	Asp	Gly
	210					215					220				
Phe	Ser	Leu	Met	Thr	Tyr	Asp	Tyr	Ser	Thr	Ala	His	Gln	Pro	Gly	Pro
225					230					235					240
Asn	Ala	Pro	Leu	Ser	Trp	Val	Arg	Ala	Cys	Val	Gln	Val	Leu	Asp	Pro
				245					250					255	
Lys	Ser	Lys	Trp	Arg	Ser	Lys	Ile	Leu	Leu	Gly	Leu	Asn	Phe	Tyr	Gly
			260					265					270		
Met	Asp	Tyr	Ala	Thr	Ser	Lys	Asp	Ala	Arg	Glu	Pro	Val	Val	Gly	Ala
		275					280					285			
Arg	Tyr	Ile	Gln	Thr	Leu	Lys	Asp	His	Arg	Pro	Arg	Met	Val	Trp	Asp
	290					295					300				
Ser	Gln	Xaa	Ser	Glu	His	Phe	Phe	Glu	Tyr	Lys	Lys	Ser	Arg	Ser	Gly
305					310					315					320
Arg	His	Val	Val	Phe	Tyr	Pro	Thr	Leu	Lys	Ser	Leu	Gln	Val	Arg	Leu
				325					330					335	
Glu	Leu	Ala	Arg	Glu	Leu	Gly	Val	Gly	Val	Ser	Ile	Trp	Glu	Leu	Gly
		340						345					350		
Gln	Gly	Leu	Asp	Tyr	Phe	Tyr	Asp	Leu	Leu	Xaa					
		355					360								

SUBSTITUTE SHEET (RULE 26)

<210> 235  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (29)  
 <223> Xaa equals stop translation

<400> 235  
 Met Cys Met Cys Val Leu Leu Cys Val Phe Leu Ile Cys Lys Tyr Ser  
           1                  5                  10                  15  
 Lys Ser Phe Leu Ile Leu Arg Leu Lys Phe Ser Cys Xaa  
                   20                  25

<210> 236  
 <211> 67  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (67)  
 <223> Xaa equals stop translation

<400> 236  
 Met Gly Asn Ala Cys Ile Pro Leu Lys Arg Ile Ala Tyr Phe Leu Cys  
           1                  5                  10                  15  
 Leu Leu Ser Ala Leu Leu Leu Thr Glu Gly Lys Lys Pro Ala Asn Gln  
                   20                  25                  30  
 Asn Ala Leu Pro Cys Val Leu Val Pro Lys Ile Met Leu Tyr Val Arg  
           35                  40                  45  
 Met Pro Asp Pro Phe His Ala Pro Phe Leu Leu Met Leu Ser His Tyr  
           50                  55                  60  
 Pro Leu Xaa  
           65

<210> 237  
 <211> 114  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (114)  
 <223> Xaa equals stop translation

<400> 237  
 Met Ile Leu Ser Leu Leu Phe Ser Leu Gly Gly Pro Leu Gly Trp Gly

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140  
 1                      5                      10                      15  
 Leu Leu Gly Ala Trp Ala Gln Ala Ser Ser Thr Ser Leu Ser Asp Leu  
                     20                      25                      30  
 Gln Ser Ser Arg Thr Pro Gly Val Trp Lys Ala Glu Ala Glu Asp Thr  
                     35                      40                      45  
 Ser Lys Asp Pro Val Gly Arg Asn Trp Cys Pro Tyr Pro Met Ser Lys  
                     50                      55                      60  
 Leu Val Thr Leu Leu Ala Leu Cys Lys Thr Glu Lys Phe Leu Ile His  
                     65                      70                      75                      80  
 Ser Gln Gln Pro Cys Pro Gln Glu Leu Gln Thr Ala Arg Lys Ser Lys  
                     85                      90                      95  
 Ser Cys Thr Ala Trp Pro Thr Ser Gln Cys Thr Arg Ser Ser Arg Arg  
                     100                      105                      110  
 Cys Xaa

<210> 238  
 <211> 106  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (106)  
 <223> Xaa equals stop translation

<400> 238  
 Met Ala Ile His Lys Ala Leu Val Met Cys Leu Gly Leu Pro Leu Phe  
                     1                      5                      10                      15  
 Leu Phe Pro Gly Ala Trp Ala Gln Gly His Val Pro Pro Gly Cys Ser  
                     20                      25                      30  
 Gln Gly Leu Asn Pro Leu Tyr Tyr Asn Leu Cys Asp Arg Ser Gly Ala  
                     35                      40                      45  
 Trp Gly Ile Val Leu Glu Ala Val Ala Gly Ala Gly Ile Val Thr Thr  
                     50                      55                      60  
 Phe Val Leu Thr Ile Ile Leu Val Ala Ser Leu Pro Phe Val Gln Asp  
                     65                      70                      75                      80  
 Thr Lys Lys Arg Ser Leu Leu Gly Thr Gln Leu Arg Gly Arg Cys His  
                     85                      90                      95  
 His Thr Ala Gly Thr Met Gly Ser Cys Xaa  
                     100                      105

SUBSTITUTE SHEET (RULE 26)

141

<210> 239  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

<400> 239  
 Gly Leu Gly Pro Ala Gln Val Ala Leu Ser Leu Gln Gly Pro Ala  
     1                    5                    10                    15

<210> 240  
 <211> 82  
 <212> PRT  
 <213> Homo sapiens

<400> 240  
 Ser Ser Trp Met Ala Gly Thr Gln Pro Arg Thr Ser Trp Trp Glu Met  
     1                    5                    10                    15

Ser Ser Ala Lys Pro Cys Pro Thr Gly Thr Leu Arg Ser Asn Thr Ser  
                     20                    25                    30

Ser His Pro Gln Cys Thr Gly Pro Pro Thr Thr His Pro Met Leu Val  
             35                    40                    45

Gly Glu Asp Met Ser Cys Pro Glu Pro Gln Cys Gly Ala Ser Arg Leu  
     50                    55                    60

Ser Trp Lys Met Leu Asn Ser Ser Pro Leu Met Met Ser Leu Trp Val  
     65                    70                    75                    80

Cys Ala

<210> 241  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 241  
 Gln Pro Arg Thr Ser Trp Trp Glu Met Ser Ser Ala Lys Pro Cys Pro  
     1                    5                    10                    15

Thr Gly Thr Leu Arg Ser Asn  
             20

<210> 242  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 242  
 Met Ser Cys Pro Glu Pro Gln Cys Gly Ala Ser Arg Leu Ser Trp Lys  
     1                    5                    10                    15

**SUBSTITUTE SHEET (RULE 26)**

142

Met Leu Asn Ser Ser Pro Leu  
20

<210> 243  
<211> 98  
<212> PRT  
<213> Homo sapiens

<400> 243  
Trp Val Ala Leu Tyr Ile Glu Gly Gly Met Lys Tyr Leu Thr Leu Val  
1 5 10 15

Phe Leu Leu Gly Arg Ala Trp Arg Met Thr Ser Pro Thr Arg Arg Ser  
20 25 30

Trp Ala Gly Ser Gln Pro Ser Arg Asn Ser Asn Thr Leu Gly Thr Trp  
35 40 45

Thr Lys Thr Ser Ser Ser Pro Phe Ser Met Lys Trp Ala Trp Gly Gln  
50 55 60

Ala Ala Thr Thr Gln Arg Cys Arg Cys Ser Ser Leu Ser Val Arg Leu  
65 70 75 80

Lys Lys Ser Ser Val Lys Ser His Trp Arg Met Ser Ser Asn Ser Leu  
85 90 95

Leu Ser

<210> 244  
<211> 20  
<212> PRT  
<213> Homo sapiens

<400> 244  
Gly Gly Met Lys Tyr Leu Thr Leu Val Phe Leu Leu Gly Arg Ala Trp  
1 5 10 15

Arg Met Thr Ser  
20

<210> 245  
<211> 25  
<212> PRT  
<213> Homo sapiens

<400> 245  
Ser Gln Pro Ser Arg Asn Ser Asn Thr Leu Gly Thr Trp Thr Lys Thr  
1 5 10 15

Ser Ser Ser Pro Phe Ser Met Lys Trp  
20 25

**SUBSTITUTE SHEET (RULE 26)**



<210> 246  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 246  
 Thr Thr Gln Arg Cys Arg Cys Ser Ser Leu Ser Val Arg Leu Lys Lys  
           1                          5                          10                          15  
 Ser Ser Val Lys Ser His Trp Arg Met Ser  
                           20                          25

<210> 247  
 <211> 223  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (13)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (14)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (15)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (27)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (108)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (113)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (117)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (121)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (122)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (125)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (129)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (130)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 247

Ala	Ser	Thr	Leu	Ala	Gln	Thr	Thr	Gly	Thr	Cys	Lys	Xaa	Xaa	Xaa	Ser
1				5				10						15	

Ser	Arg	Arg	Ala	Arg	Ser	Arg	Thr	Gln	Arg	Xaa	Phe	Gln	Leu	Arg	Pro
			20					25					30		

Asp	Lys	Arg	Ser	Ala	Pro	Ser	Leu	Leu	Gln	Phe	Ile	Gln	Ala	Gln	Glu
			35				40					45			

Glu	Leu	Ser	Lys	Glu	Asn	Thr	Gly	Arg	Gln	Leu	Ala	Ala	Arg	Glu	Ala
	50					55					60				

Val	Leu	Ala	Leu	Glu	Gly	Ser	Thr	Gln	Leu	Thr	Gly	Pro	Val	Thr	Gln
	65				70					75					80

Val	Ala	Ala	Ser	Lys	Thr	His	Cys	Ser	Gly	Met	Ala	Leu	Thr	Ala	Ser
				85					90					95	

Pro	Val	Pro	Val	Leu	Gly	Ala	Ala	Pro	Ala	Lys	Xaa	Pro	Thr	Gln	Asn
			100					105					110		

Xaa	Pro	Gly	Gln	Xaa	Gly	Arg	Ala	Xaa	Xaa	Lys	Val	Xaa	Thr	Ser	Trp
		115				120						125			

Xaa	Xaa	Val	Ala	Thr	Lys	Val	Leu	His	Gly	Leu	Glu	Val	Ser	Thr	His
		130				135					140				

Leu	Gly	Lys	Arg	Lys	Leu	Ser	Gly	Arg	Ser	Trp	Leu	Pro	Gly	Pro	Ala
145					150				155						160

Leu	His	Ala	Thr	Pro	Ser	Gln	Ser	His	Thr	Gln	Thr	Gly	Ser	Gln	Ile
				165					170					175	

Val	His	Pro	Pro	Gln	Gly	Glu	Val	Arg	Glu	Val	Gly	Arg	Gly	Arg	Gly
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

# SUBSTITUTE SHEET (RULE 26)

**SUBSTITUTE SHEET (RULE 26)**

Cys Val Pro Thr Asn Gly Gln Pro Leu Arg Ser Cys Ser Leu Ser Lys  
 100 105 110

Leu Arg Arg Ser Phe Leu Lys Arg Thr Gln Gly Asp Ser Trp Leu Pro  
 115 120 125

Glu Lys Gln Ser Trp Leu Trp Lys Ala Pro Pro Ser  
 130 135 140

<210> 249  
 <211> 122  
 <212> PRT  
 <213> Homo sapiens

<400> 249  
 Ser His Gln Ser His Leu Ile Asn Pro Ala Ser Ser Ala Lys Gly Ser  
 1 5 10 15

Trp Ala Gln Leu Lys Ala Gln Pro Pro Ala His Val Leu Gly Gly Thr  
 20 25 30

Gly Gln Glu Gly Pro Pro Pro Thr Ala Asp Gln Pro Glu Ser Pro Gly  
 35 40 45

Trp Asp Pro Ser Ser Phe Thr Asn Gly Ser Ser Gly Pro Arg Ala Leu  
 50 55 60

Pro Thr Ser Val His Pro Thr Leu Gln Gln Gly Ala Pro Cys Arg Arg  
 65 70 75 80

Asn Trp Ala Pro Cys Arg Gly Leu Val Glu Thr Arg Met Leu Arg Arg  
 85 90 95

Gln Leu Pro His Gly Thr Ser Lys Arg Asp Leu Gly Trp Ala Ser Leu  
 100 105 110

Gln Arg Gly Ser Pro Gln Glu Thr Pro Gln  
 115 120

<210> 250  
 <211> 35  
 <212> PRT  
 <213> Homo sapiens

<400> 250  
 Arg Pro Asp Lys Arg Ser Ala Pro Ser Leu Leu Gln Phe Ile Gln Ala  
 1 5 10 15

Gln Glu Glu Leu Ser Lys Glu Asn Thr Gly Arg Gln Leu Ala Ala Arg  
 20 25 30

Glu Ala Val  
 35

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<210> 251  
<211> 33  
<212> PRT  
<213> Homo sapiens

<400> 251  
Ala Thr Pro Ser Gln Ser His Thr Gln Thr Gly Ser Gln Ile Val His  
1 5 10 15  
Pro Pro Gln Gly Glu Val Arg Glu Val Gly Arg Gly Arg Gly Gln Pro  
20 25 30  
Pro

<210> 252  
<211> 29  
<212> PRT  
<213> Homo sapiens

<400> 252  
Gln Asp Ser Gln His Ser Pro Pro His Val Arg Ala His Leu Leu Ile  
1 5 10 15  
Ser Pro Leu Pro Ala Phe Pro Ser Met Gly Gly Pro Ala  
20 25

<210> 253  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 253  
Asp Ser Phe Asn Cys Val Pro Thr Asn Gly Gln Pro Leu Arg Ser Cys  
1 5 10 15  
Ser Leu Ser Lys Leu Arg Arg Ser Phe Leu Lys Arg  
20 25

<210> 254  
<211> 25  
<212> PRT  
<213> Homo sapiens

<400> 254  
Lys Gly Ser Trp Ala Gln Leu Lys Ala Gln Pro Pro Ala His Val Leu  
1 5 10 15  
Gly Gly Thr Gly Gln Glu Gly Pro Pro  
20 25

<210> 255

148

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 255

Ala Pro Ser Leu Leu Gln Phe Ile Gln Ala Gln Glu Glu Leu Ser Lys  
1 5 10 15

Glu Asn Thr Gly Arg Gln Leu Ala Ala Arg  
20 25

&lt;210&gt; 256

&lt;211&gt; 6

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 256

Lys Pro Ser His Gln Pro  
1 5

&lt;210&gt; 257

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 257

Cys Ser Tyr Arg Pro Gln Phe Pro Val Asp Pro Arg Val Arg Ala Thr  
1 5 10 15

Cys Ile Val Phe Asn  
20

&lt;210&gt; 258

&lt;211&gt; 128

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (46)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (60)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (66)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 258

Gly Thr Glu Asn Leu Leu Ala Pro Glu Arg Thr Ile Leu Ser Arg Ala

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149

1	5	10	15
Gln Met Gly Lys Cys Met Ala Thr Pro Ala Pro Cys Val Arg Ser Ser	20	25	30
Ser Lys Gln Lys Lys Lys Lys Arg Lys Arg Arg Lys Val Xaa Gln Glu	35	40	45
Thr Lys Asp Asn Leu Arg Val Gln Leu Pro Leu Xaa Ser Cys Val Val	50	55	60
Asn Xaa Ala Asn Pro Gly Lys Thr Asp Gly Phe Phe Ala Pro Glu Arg	65	70	75
Met Thr Pro Ser Arg Ala Gln Met Glu Lys Cys Met Ala Thr Pro Ala	85	90	95
Pro Cys Val Arg Pro Ser Phe Asn Lys Lys Lys Glu Gln Glu Gln Arg	100	105	110
Leu Lys Glu Lys Leu Gln Arg Lys Ser Ala Val Asn Phe Gly Thr Lys	115	120	125

<210> 259  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 259  
 Leu Leu Ala Pro Glu Arg Thr Ile Leu Ser Arg Ala Gln Met Gly Lys  
 1 5 10 15  
 Cys Met Ala Thr Pro Ala Pro Cys Val Arg  
 20 25

<210> 260  
 <211> 24  
 <212> PRT  
 <213> Homo sapiens

<400> 260  
 Pro Gly Lys Thr Asp Gly Phe Phe Ala Pro Glu Arg Met Thr Pro Ser  
 1 5 10 15  
 Arg Ala Gln Met Glu Lys Cys Met  
 20

<210> 261  
 <211> 17  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 261

Glu Gln Arg Leu Lys Glu Lys Leu Gln Arg Lys Ser Ala Val Asn Phe  
 1 5 10 15

Gly

&lt;210&gt; 262

&lt;211&gt; 186

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (42)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (68)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (69)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 262

Lys Thr Leu Leu Glu Asn Phe Ser Thr Gln Gly Thr Phe Val Ala Met  
 1 5 10 15

His Pro Ala Val Arg Ala Thr Asp Trp Ile Thr Leu Pro Cys Thr Lys  
 20 25 30

Lys Pro Ser Ile Ser His Leu Phe Phe Xaa Phe Leu Ala Lys Ile Leu  
 35 40 45

Phe Ser Ile Ser Ser Asn Ser Ser Phe Thr Leu Ser Leu Gly Ile Phe  
 50 55 60

Ser Phe Phe Xaa Xaa Gln Leu Ser Thr His Cys Thr Leu Ile Ala Met  
 65 70 75 80

Arg Leu Pro Ile Arg Thr Lys Asn Arg Ile Ile Phe Pro Cys Ala Ser  
 85 90 95

Lys Ser Ser Ile Ser Asn Lys Gly Pro Lys Ser Thr Ala Tyr Ile Leu  
 100 105 110

Leu Trp Ile Thr Ala Leu Thr Phe Pro Phe Thr Phe Tyr Thr Asn Leu  
 115 120 125

Gly Pro Gly Phe Arg Ile Leu Ser Thr Gln Cys Thr Ser Val Val Ile  
 130 135 140

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151

Cys Phe Pro Ile Cys Ala Thr Asn Ser Phe Ile Ile Ile Arg Thr Asp  
 145 150 155 160

Lys Ile Pro Ile Ser Phe Ser Phe Phe Lys Ile Ile Thr Ile Gln Leu  
 165 170 175

Cys Trp Gly Ser Ser Leu Gly Ser Ser Cys  
 180 185

&lt;210&gt; 263

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 263

Met His Pro Ala Val Arg Ala Thr Asp Trp Ile Thr Leu Pro Cys Thr  
 1 5 10 15

Lys Lys Pro Ser Ile Ser  
 20

&lt;210&gt; 264

&lt;211&gt; 17

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 264

Leu Ile Ala Met Arg Leu Pro Ile Arg Thr Lys Asn Arg Ile Ile Phe  
 1 5 10 15

Pro

&lt;210&gt; 265

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 265

Ser Ser Ile Ser Asn Lys Gly Pro Lys Ser Thr Ala Tyr Ile Leu Leu  
 1 5 10 15

Trp Ile Thr Ala Leu Thr Phe Pro Phe Thr  
 20 25

&lt;210&gt; 266

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 266

Ile Ile Ile Arg Thr Asp Lys Ile Pro Ile Ser Phe Ser Phe Phe Lys  
 1 5 10 15

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Ile Ile Thr Ile Gln Leu Cys  
20

<210> 267

<211> 165

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (147)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (153)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 267

Asn Asp Gly Gln Cys Leu Ala Tyr Asn Thr Thr His Tyr Arg Glu Arg  
1 5 10 15

Ala Met Thr Ser His Ala Arg Val Ser Leu Gly Pro Ser Arg Asp Pro  
20 25 30

Leu Glu Arg Pro Pro Phe Phe Phe Phe Phe Phe Phe Phe Phe Phe  
35 40 45

Lys Phe Glu His Thr Gly Thr His Gly Thr Leu Val Ser Met His Phe  
50 55 60

Ala Ile Trp Ala Thr Asp Arg Ile Met Leu Pro Gly Ala Tyr Lys Cys  
65 70 75 80

Ser Ile Pro His Leu Val Pro Lys Phe Thr Ala Asp Phe Leu Cys Ser  
85 90 95

Phe Ser Phe Ser Leu Cys Ser Cys Ser Phe Phe Leu Leu Lys Glu Gly  
100 105 110

Leu Thr His Gly Ala Gly Val Ala Met His Phe Ser Ile Trp Ala Leu  
115 120 125

Asp Gly Val Ile Leu Ser Gly Ala Lys Lys Pro Ser Val Phe Pro Gly  
130 135 140

Phe Ala Xaa Phe Thr Thr Gln Leu Xaa Lys Gly Ser Cys Thr Leu Arg  
145 150 155 160

Leu Ser Phe Val Ser  
165

<210> 268

<211> 22

**SUBSTITUTE SHEET (RULE 26)**

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 268

Cys Leu Ala Tyr Asn Thr Thr His Tyr Arg Glu Arg Ala Met Thr Ser  
 1 5 10 15

His Ala Arg Val Ser Leu  
 20

&lt;210&gt; 269

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 269

Gly Thr Leu Val Ser Met His Phe Ala Ile Trp Ala Thr Asp Arg Ile  
 1 5 10 15

Met Leu Pro Gly Ala Tyr Lys Cys Ser Ile Pro His Leu Val Pro  
 20 25 30

&lt;210&gt; 270

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (18)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (24)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 270

Gly Val Ile Leu Ser Gly Ala Lys Lys Pro Ser Val Phe Pro Gly Phe  
 1 5 10 15

Ala Xaa Phe Thr Thr Gln Leu Xaa  
 20

&lt;210&gt; 271

&lt;211&gt; 141

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (26)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

SUBSTITUTE SHEET (RULE 26)

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (38)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (44)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (57)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (58)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 271

Lys	Lys	Ala	Ser	His	Met	Glu	Gln	Val	Leu	Pro	Cys	Ile	Phe	Pro	Ser
1				5					10					15	

Gly	Pro	Trp	Met	Gly	Ser	Phe	Ser	Leu	Xaa	Gln	Lys	Ser	Arg	Pro	Phe
			20					25					30		

Phe	Leu	Asp	Leu	Arg	Xaa	Ser	Leu	His	Asn	Ser	Xaa	Lys	Glu	Ala	Val
		35					40					45			

Leu	Leu	Asp	Cys	Leu	Leu	Phe	Leu	Xaa	Xaa	Pro	Ser	Phe	Phe	Phe	Phe
	50					55					60				

Ser	Ser	Ser	Ser	Ala	Trp	Lys	Lys	Thr	Ser	His	Met	Glu	Gln	Val	Leu
65					70					75					80

Pro	Cys	Thr	Phe	Pro	Ser	Gly	Pro	Trp	Ile	Gly	Leu	Phe	Ser	Leu	Val
				85					90					95	

Gln	Ala	Ser	Phe	Pro	Phe	Leu	Thr	Ser	Phe	Arg	Tyr	Ser	Leu	Gln	Ser
		100						105					110		

Ser	Ala	Tyr	Glu	Val	Ala	Phe	Pro	Asp	Ser	Leu	Leu	Phe	Leu	Ala	Arg
		115					120					125			

Ala	Ser	Ala	Phe	Phe	Phe	Ser	Ser	Phe	Ser	Ala	Trp	Lys
	130					135					140	

&lt;210&gt; 272

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (15)

SUBSTITUTE SHEET (RULE 26)

155

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (27)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 272

Cys Ile Phe Pro Ser Gly Pro Trp Met Gly Ser Phe Ser Leu Xaa Gln  
 1 5 10 15

Lys Ser Arg Pro Phe Phe Leu Asp Leu Arg Xaa Ser  
 20 25

&lt;210&gt; 273

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 273

Trp Ile Gly Leu Phe Ser Leu Val Gln Ala Ser Phe Pro Phe Leu Thr  
 1 5 10 15

Ser Phe Arg Tyr Ser Leu Gln Ser Ser Ala Tyr Glu  
 20 25

&lt;210&gt; 274

&lt;211&gt; 79

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 274

Asn Ser Ala Val Asn Ile Lys Ile Arg Gln Arg Met Glu Tyr Phe Ser  
 1 5 10 15

Val Pro Glu Lys Met Thr Leu Phe Val Val Gln Met Gly Lys Cys Met  
 20 25 30

Ala Thr Cys Val Pro Cys Val Lys Pro Thr Ser Lys Gln Lys Met Lys  
 35 40 45

Lys Arg Lys Arg Leu Lys His Glu Leu Glu Thr Lys Glu Asn Leu Glu  
 50 55 60

Lys Gln Pro His Met Gln Ser Phe Ala Val Asn Ile Glu Ser Leu  
 65 70 75

&lt;210&gt; 275

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 275

Ile Lys Ile Arg Gln Arg Met Glu Tyr Phe Ser Val Pro Glu Lys Met

SUBSTITUTE SHEET (RULE 26)

156  
 1 5 10 15  
 Thr Leu Phe Val Val Gln Met  
 20

<210> 276  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<400> 276  
 Val Lys Pro Thr Ser Lys Gln Lys Met Lys Lys Arg Lys Arg Leu Lys  
 1 5 10 15

His Glu Leu Glu Thr Lys Glu Asn Leu  
 20 25

<210> 277  
 <211> 63  
 <212> PRT  
 <213> Homo sapiens

<400> 277  
 Pro Arg Val Arg Gly Thr Val Val Arg Leu Arg Gln His Arg Pro Ser  
 1 5 10 15

Ala Tyr Ile Leu Val Ser Thr Val Leu Thr Leu Met Val Pro Trp His  
 20 25 30

Ser Leu Asp Pro Asp Ser Ala Leu Ala Asp Ala Phe Tyr Gln Arg Gly  
 35 40 45

Tyr Arg Trp Ala Gly Phe Ile Val Ala Ala Gly Ser Ile Cys Ala  
 50 55 60

<210> 278  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<400> 278  
 Thr Val Val Arg Leu Arg Gln His Arg Pro Ser Ala Tyr Ile Leu Val  
 1 5 10 15

Ser Thr Val Leu Thr Leu Met Val Pro  
 20 25

<210> 279  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 279

SUBSTITUTE SHEET (RULE 26)

157

Trp His Ser Leu Asp Pro Asp Ser Ala Leu Ala Asp Ala Phe Tyr Gln  
 1 5 10 15

Arg Gly Tyr Arg Trp Ala Gly Phe Ile Val  
 20 25

&lt;210&gt; 280

&lt;211&gt; 101

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 280

Thr Pro Ser Cys Ser Ala Ser Ser Ser Pro Cys His Ala Leu Ser Met  
 1 5 10 15

Pro Trp Pro Pro Met Gly Ser Ser Ser Arg Cys Leu Pro Met Cys Thr  
 20 25 30

Pro Gly His Arg Cys Leu Trp Arg Ala Pro Trp Arg Ser Gly Ser Ser  
 35 40 45

Arg Pro Ser Trp His Cys Cys Trp Thr Trp Ser Arg Trp Phe Ser Ser  
 50 55 60

Cys Pro Leu Ala His Ser Trp Pro Thr His Ser Trp Pro Pro Val Ser  
 65 70 75 80

Leu Cys Cys Ala Ser Arg Ser Leu Pro Arg Pro Ala Pro Gln Ala Gln  
 85 90 95

Pro Ala Leu Ala Pro  
 100

&lt;210&gt; 281

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 281

Leu Ser Met Pro Trp Pro Pro Met Gly Ser Ser Ser Arg Cys Leu Pro  
 1 5 10 15

Met Cys Thr Pro Gly His Arg Cys  
 20

&lt;210&gt; 282

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 282

Ala Pro Trp Arg Ser Gly Ser Ser Arg Pro Ser Trp His Cys Cys Trp  
 1 5 10 15

SUBSTITUTE SHEET (RULE 26)

158

Thr Trp Ser Arg Trp Phe Ser Ser Cys Pro Leu  
                   20                  25

<210> 283  
 <211> 22  
 <212> PRT  
 <213> Homo sapiens

<400> 283  
 Thr His Ser Trp Pro Pro Val Ser Leu Cys Cys Ala Ser Arg Ser Leu  
   1                                  5                  10                  15

Pro Arg Pro Ala Pro Gln  
                   20

<210> 284  
 <211> 60  
 <212> PRT  
 <213> Homo sapiens

<400> 284  
 Ala Tyr Ile Leu Val Ser Thr Val Leu Thr Leu Met Val Pro Trp His  
   1                                  5                  10                  15

Ser Leu Asp Pro Asp Ser Ala Leu Ala Asp Ala Phe Tyr Gln Arg Gly  
                   20                  25                  30

Tyr Arg Trp Ala Gly Phe Ile Val Ala Ala Gly Ser Ile Cys Ala Met  
                   35                  40                  45

Asn Thr Val Leu Leu Ser Leu Leu Phe Ser Leu Pro  
   50                                  55                  60

<210> 285  
 <211> 31  
 <212> PRT  
 <213> Homo sapiens

<400> 285  
 Pro Trp His Ser Leu Asp Pro Asp Ser Ala Leu Ala Asp Ala Phe Tyr  
   1                                  5                  10                  15

Gln Arg Gly Tyr Arg Trp Ala Gly Phe Ile Val Ala Ala Gly Ser  
                   20                  25                  30

<210> 286  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 286  
 Arg Ile Val Tyr Ala Met Ala Ala Asp Gly Leu Phe Phe Gln Val Phe  
   1                                  5                  10                  15

SUBSTITUTE SHEET (RULE 26)



Ala His Val His Pro Arg Thr Gln Val Pro Val  
                   20                                  25

<210> 287  
 <211> 16  
 <212> PRT  
 <213> Homo sapiens

<400> 287  
 Asp Leu Glu Ser Leu Val Gln Phe Leu Ser Leu Gly Thr Leu Leu Ala  
       1                                  5                                  10                                  15

<210> 288  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

<400> 288  
 Tyr Thr Phe Val Ala Thr Ser Ile Ile Val Leu Arg Phe Gln Lys  
       1                                  5                                  10                                  15

<210> 289  
 <211> 31  
 <212> PRT  
 <213> Homo sapiens

<400> 289  
 Leu Thr Lys Gln Gln Ser Ser Phe Ser Asp His Leu Gln Leu Val Gly  
       1                                  5                                  10                                  15

Thr Val His Ala Ser Val Pro Glu Pro Gly Glu Leu Lys Pro Ala  
                   20                                  25                                  30

<210> 290  
 <211> 50  
 <212> PRT  
 <213> Homo sapiens

<400> 290  
 Leu Arg Pro Tyr Leu Gly Phe Leu Asp Gly Tyr Ser Pro Gly Ala Val  
       1                                  5                                  10                                  15

Val Thr Trp Ala Leu Gly Val Met Leu Ala Ser Ala Ile Thr Ile Gly  
                   20                                  25                                  30

Cys Val Leu Val Phe Gly Asn Ser Thr Leu His Leu Pro His Trp Gly  
           35                                  40                                  45

Tyr Ile

**SUBSTITUTE SHEET (RULE 26)**

160

50

<210> 291  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 291  
 Pro Gly Ala Val Val Thr Trp Ala Leu Gly Val Met Leu Ala Ser Ala  
           1                          5                          10                          15

Ile Thr Ile Gly Cys Val Leu Val Phe Gly Asn  
                           20                          25

<210> 292  
 <211> 53  
 <212> PRT  
 <213> Homo sapiens

<400> 292  
 Gly Ala His Gln Gln Gln Tyr Arg Glu Asp Leu Phe Gln Ile Pro Met  
           1                          5                          10                          15

Val Pro Leu Ile Pro Ala Leu Ser Ile Val Leu Asn Ile Cys Leu Met  
                           20                          25                          30

Leu Lys Leu Ser Tyr Leu Thr Trp Val Arg Phe Ser Ile Trp Leu Leu  
                           35                          40                          45

Met Gly Leu Ala Val  
           50

<210> 293  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 293  
 Met Val Pro Leu Ile Pro Ala Leu Ser Ile Val Leu Asn Ile Cys Leu  
           1                          5                          10                          15

Met Leu Lys Leu Ser Tyr Leu Thr Trp Val  
                           20                          25

<210> 294  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<400> 294  
 Tyr Phe Gly Tyr Gly Ile Arg His Ser Lys Glu Asn Gln Arg Glu Leu  
           1                          5                          10                          15

SUBSTITUTE SHEET (RULE 26)

161

Pro Gly Leu Asn Ser Thr His Tyr Val Val Phe Pro Arg  
                   20                  25

<210> 295  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 295  
 Phe Pro Pro Ser Pro Ala Pro Pro His Ser Leu Pro Leu Arg Ser Trp  
   1                  5                  10                  15

Leu Trp Ser Arg Gln Met Gly  
                   20

<210> 296  
 <211> 148  
 <212> PRT  
 <213> Homo sapiens

<400> 296  
 Gly Thr Ser Phe Arg Gly Met Ile Ser Thr Gln Pro Gly Ser Thr Pro  
   1                  5                  10                  15

Leu Ala Ser Phe Lys Ile Leu Ala Leu Glu Ser Ala Asp Gly His Gly  
                   20                  25                  30

Gly Cys Ser Ala Gly Asn Asp Ile Gly Pro Tyr Gly Glu Arg Asp Asp  
                   35                  40                  45

Gln Gln Val Phe Ile Gln Lys Val Val Pro Ser Ala Ser Gln Leu Phe  
                   50                  55                  60

Val Arg Leu Ser Ser Thr Gly Gln Arg Val Cys Ser Val Arg Ser Val  
   65                  70                  75                  80

Asp Gly Ser Pro Thr Thr Ala Phe Thr Val Leu Glu Cys Glu Gly Ser  
                   85                  90                  95

Pro Ala Ala Arg Leu Ser Ala Pro Ala Leu Pro Ala His Trp Pro Gly  
                   100                  105                  110

Gln Arg Gln Leu Gly His Val Gly Pro Asn His Arg His Gly Arg Pro  
                   115                  120                  125

Arg Pro Gly Pro Cys Arg Trp Pro Asp Gly Ala Arg Ala Asp Gly Thr  
                   130                  135                  140

Ala Gly Thr Leu  
 145

<210> 297  
 <211> 29  
 <212> PRT

SUBSTITUTE SHEET (RULE 26)

162

&lt;213&gt; Homo sapiens

&lt;400&gt; 297

Pro Gly Ser Thr Pro Leu Ala Ser Phe Lys Ile Leu Ala Leu Glu Ser  
1 5 10 15

Ala Asp Gly His Gly Gly Cys Ser Ala Gly Asn Asp Ile  
20 25

&lt;210&gt; 298

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 298

Gly Glu Arg Asp Asp Gln Gln Val Phe Ile Gln Lys Val Val Pro Ser  
1 5 10 15

Ala Ser Gln Leu Phe Val Arg Leu  
20

&lt;210&gt; 299

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 299

Arg Ser Val Asp Gly Ser Pro Thr Thr Ala Phe Thr Val Leu Glu Cys  
1 5 10 15

Glu Gly Ser Pro Ala Ala Arg Leu Ser  
20 25

&lt;210&gt; 300

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 300

Pro Ala Leu Pro Ala His Trp Pro Gly Gln Arg Gln Leu Gly His Val  
1 5 10 15

Gly Pro Asn His Arg His Gly Arg Pro Arg  
20 25

&lt;210&gt; 301

&lt;211&gt; 168

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 301

Pro Phe Ile Pro Arg Arg Pro Trp Pro Glu Pro Gly Val Pro Thr Gly  
1 5 10 15

SUBSTITUTE SHEET (RULE 26)

163

Ile Arg Glu Ala Pro Glu Ser Pro Arg Thr Arg Ala Ser Gln Gly Ile  
                   20                                  25                                  30  
 Met Ala Ala Ala Leu Phe Lys Lys Glu Val Ser Leu Ser Phe Ile Leu  
                   35                                  40                                  45  
 Gly Gly Val Arg Gly Val Pro Arg Pro Leu Glu Gly His Gly Ala Gly  
                   50                                  55                                  60  
 Val Gly Gly Arg Arg Arg Ser Gly Pro Leu Arg Thr Ser Ser Trp Gln  
                   65                                  70                                  75                                  80  
 Arg Ser Thr Lys Leu Pro Pro Pro Arg Arg Arg Ala Ser Ala Cys Gly  
                   85                                  90                                  95  
 Gly Leu Gly Leu Pro Arg Trp Pro Asp Lys Glu Val Leu Leu Glu Ala  
                   100                                  105                                  110  
 Glu Trp Arg Leu Val Arg Glu Met Arg Gly Glu Gly Leu Gly Arg Gln  
                   115                                  120                                  125  
 Pro His Glu Gly Ala Glu Arg Ser Arg Arg Gly Gln Leu Thr Val Phe  
                   130                                  135                                  140  
 Gln Leu Phe His Gln Leu Leu Leu Arg Gln Ala Thr Cys Arg Gly Leu  
                   145                                  150                                  155                                  160  
 Ala Glu Ala Val His Gly Gly Gly  
                   165

&lt;210&gt; 302

&lt;211&gt; 32

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 302

Pro Gly Val Pro Thr Gly Ile Arg Glu Ala Pro Glu Ser Pro Arg Thr  
   1                                  5                                  10                                  15

Arg Ala Ser Gln Gly Ile Met Ala Ala Ala Leu Phe Lys Lys Glu Val  
                   20                                  25                                  30

&lt;210&gt; 303

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 303

Phe Ile Leu Gly Gly Val Arg Gly Val Pro Arg Pro Leu Glu Gly His  
   1                                  5                                  10                                  15

SUBSTITUTE SHEET (RULE 26)

164

Gly Ala Gly Val Gly Gly Arg Arg Arg Ser Gly Pro  
                   20                                  25

<210> 304  
 <211> 24  
 <212> PRT  
 <213> Homo sapiens

<400> 304  
 Gly Leu Pro Arg Trp Pro Asp Lys Glu Val Leu Leu Glu Ala Glu Trp  
       1                                  5                                  10                                  15

Arg Leu Val Arg Glu Met Arg Gly  
                   20

<210> 305  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 305  
 Gly Ala Glu Arg Ser Arg Arg Gly Gln Leu Thr Val Phe Gln Leu Phe  
       1                                  5                                  10                                  15

His Gln Leu Leu Leu Arg Gln  
                   20

<210> 306  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

<400> 306  
 His Ala Ser Ala His Ala Ser Ala His Ala Ser Gly Cys Gly Ala  
       1                                  5                                  10                                  15

<210> 307  
 <211> 118  
 <212> PRT  
 <213> Homo sapiens

<400> 307  
 Gln Gly Val Gly Val Ala Asp Glu Gly Gly Leu Glu Arg Gln Arg Val  
       1                                  5                                  10                                  15

Asp Ala Gly Ala Arg Leu Gly His Met Gly Gln Pro Val Ala Phe Ser  
                   20                                  25                                  30

Thr Arg Gln Leu His Leu Ala Leu Pro Ala Pro Gly Thr Ala Gly Val  
                   35                                  40                                  45

Thr Val Pro His Pro His Ala Arg Glu Gly Val Val Gly Asp Leu Pro  
                   50                                  55                                  60

SUBSTITUTE SHEET (RULE 26)

Leu Val Pro Asp Ala Glu Asp Pro Thr Val Gly Val Pro Ala Glu Gly  
 65 70 75 80  
 Leu Leu Val Leu Gly His Val Val Glu Arg Ala Glu Leu Ile Leu Val  
 85 90 95  
 Arg Gly Leu His Gln Ala Glu Ala Leu Ala Arg Glu Ser Glu Glu Met  
 100 105 110  
 His Gly Ser Arg His Gly  
 115

<210> 308  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<400> 308  
 Glu Gly Gly Leu Glu Arg Gln Arg Val Asp Ala Gly Ala Arg Leu Gly  
 1 5 10 15  
 His Met Gly Gln Pro Val Ala Phe Ser  
 20 25

<210> 309  
 <211> 29  
 <212> PRT  
 <213> Homo sapiens

<400> 309  
 Leu Ala Leu Pro Ala Pro Gly Thr Ala Gly Val Thr Val Pro His Pro  
 1 5 10 15  
 His Ala Arg Glu Gly Val Val Gly Asp Leu Pro Leu Val  
 20 25

<210> 310  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 310  
 Pro Ala Glu Gly Leu Leu Val Leu Gly His Val Val Glu Arg Ala Glu  
 1 5 10 15  
 Leu Ile Leu Val Arg Gly Leu His Gln Ala Glu Ala  
 20 25

<210> 311  
 <211> 125  
 <212> PRT  
 <213> Homo sapiens

**SUBSTITUTE SHEET (RULE 26)**

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (32)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 311

His Leu Phe Lys Phe Phe Tyr Thr Ile Ala Phe Met Gln Trp Phe Thr  
 1 5 10 15

Glu Phe Met Glu Leu Phe Leu Ser Val Trp Glu Leu Ile Lys Thr Xaa  
 20 25 30

Asn Leu Cys Phe Val Cys Phe Ser Glu His Lys Pro Gly Gln Leu Val  
 35 40 45

Pro Ala Gly Pro Thr Ser Gln Leu Leu Cys Arg Ala Leu Gly Arg Val  
 50 55 60

His Leu Cys Ser Pro Thr Thr Arg Ser Gln Thr Pro Thr Gln Ser Trp  
 65 70 75 80

Val Thr Pro Gln Leu Leu Trp Arg Leu Gly Ser Gly Arg Leu Val Ala  
 85 90 95

Gln Val Leu Gln Val Gly Ser Phe Cys Gly Pro Arg Val Gly Asp Ala  
 100 105 110

Val Leu Gly Glu Gln Thr Phe Gln Pro Phe Asp Leu Leu  
 115 120 125

&lt;210&gt; 312

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (23)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 312

Ala Phe Met Gln Trp Phe Thr Glu Phe Met Glu Leu Phe Leu Ser Val  
 1 5 10 15

Trp Glu Leu Ile Lys Thr Xaa Asn Leu Cys Phe Val Cys  
 20 25

&lt;210&gt; 313

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 313

Arg Ser Gln Thr Pro Thr Gln Ser Trp Val Thr Pro Gln Leu Leu Trp



167  
 1 5 10 15  
 Arg Leu Gly Ser Gly Arg Leu Val Ala Gln  
 20 25  
 <210> 314  
 <211> 39  
 <212> PRT  
 <213> Homo sapiens  
 <400> 314  
 Gly Ala Trp Gly Val Glu Val Val Ala Val Gly Ser Lys Ala Gly Cys  
 1 5 10 15  
 Leu Val Tyr Gln Leu Cys Asp Leu Lys Gln Ile Thr Phe Phe Phe Arg  
 20 25 30  
 Ala Ser Val Cys Leu Ser Val  
 35

<210> 315  
 <211> 194  
 <212> PRT  
 <213> Homo sapiens  
 <220>  
 <221> SITE  
 <222> (61)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (95)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (116)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (129)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (131)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
 <220>  
 <221> SITE  
 <222> (132)  
 <223> Xaa equals any of the naturally occurring L-amino acids

SUBSTITUTE SHEET (RULE 26)

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (163)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (187)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 315

Pro	Ala	Ser	Leu	Gly	Ser	Ser	Trp	Gly	Gln	Lys	Leu	Arg	Gly	Gly	Thr
1				5					10					15	

Arg	Lys	Ser	Phe	Gln	Glu	Leu	Ser	Pro	Ser	Ser	Ala	Pro	Pro	Ala	Cys
			20					25					30		

Leu	Pro	Gln	Pro	Pro	Ala	Ser	Thr	Trp	Leu	Ser	Ser	Trp	Pro	Arg	Pro
		35					40					45			

Pro	Cys	Trp	Pro	Pro	Met	Cys	Ser	Trp	Ala	Leu	Gly	Xaa	Cys	Phe	Cys
	50					55					60				

Pro	Ala	Thr	Gly	Gln	Trp	Leu	Pro	Thr	Ser	Cys	Cys	Leu	Trp	Trp	Cys
65					70					75					80

Pro	Asp	Ala	Gly	Gly	Arg	Gln	Lys	His	Phe	Arg	Ser	Arg	Trp	Xaa	Thr
				85					90					95	

Ser	Trp	Glu	Thr	Trp	Gln	Pro	Tyr	Leu	Thr	Gly	Leu	Ile	Ser	Ser	Val
		100						105					110		

Leu	Arg	Ala	Xaa	Arg	Pro	Asp	Ser	Tyr	Leu	Gln	Arg	Phe	Arg	Ser	Leu
		115					120					125			

Xaa	Gln	Xaa	Xaa	Leu	Cys	Cys	Ala	Phe	Val	Ile	Ala	Leu	Gly	Gly	Gly
	130					135					140				

Cys	Phe	Leu	Leu	Thr	Ala	Leu	Tyr	Leu	Glu	Arg	Asp	Glu	Thr	Arg	Ala
145					150					155					160

Trp	Gln	Xaa	Val	Thr	Gly	Thr	Pro	Asp	Ser	Asn	Asp	Val	Asp	Ser	Asn
			165						170					175	

Asp	Leu	Glu	Arg	Gln	Gly	Leu	Leu	Ser	Gly	Xaa	Gly	Ala	Ser	Thr	Glu
			180					185						190	

Glu Pro

&lt;210&gt; 316

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 316

169

Leu Arg Gly Gly Thr Arg Lys Ser Phe Gln Glu Leu Ser Pro Ser Ser  
 1 5 10 15

Ala Pro Pro Ala Cys Leu Pro Gln Pro Pro  
 20 25

&lt;210&gt; 317

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 317

Ala Thr Gly Gln Trp Leu Pro Thr Ser Cys Cys Leu Trp Trp Cys Pro  
 1 5 10 15

Asp Ala Gly Gly Arg Gln Lys His Phe Arg Ser Arg  
 20 25

&lt;210&gt; 318

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (21)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 318

Gly Gly Cys Phe Leu Leu Thr Ala Leu Tyr Leu Glu Arg Asp Glu Thr  
 1 5 10 15

Arg Ala Trp Gln Xaa Val  
 20

&lt;210&gt; 319

&lt;211&gt; 124

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (38)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (72)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (76)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

SUBSTITUTE SHEET (RULE 26)

<220>  
 <221> SITE  
 <222> (93)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (105)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (106)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (107)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (108)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (109)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 319  
 Ala Pro His Leu Arg Leu Gln Pro Ala Cys His Ser Pro Leu Pro Leu  
   1                  5                  10                  15  
 Pro Gly Ser Arg Pro Gly Pro Asp His Pro Ala Gly Leu Leu Cys Val  
                   20                  25                  30  
 Pro Gly Pro Trp Gly Xaa Ala Ser Val Leu Gln Leu Gly Ser Gly Cys  
                   35                  40                  45  
 Arg His Pro Ala Val Cys Gly Gly Ala Gln Met Pro Gly Asp Gly Arg  
                   50                  55                  60  
 Ser Thr Ser Asp His Gly Gly Xaa His Pro Gly Xaa Pro Gly Ser Pro  
   65                  70                  75                  80  
 Ile Ser Gln Asp Leu Ser Leu Val Ser Cys Gly Pro Xaa Ala Leu Thr  
                   85                  90                  95  
 Pro Ile Cys Ser Ala Ser Ala Ala Xaa Xaa Xaa Xaa Xaa Cys Ala Ala  
                   100                  105                  110  
 Pro Leu Ser Ser Pro Trp Gly Ala Ala Ala Ser Cys  
                   115                  120

SUBSTITUTE SHEET (RULE 26)

171

<210> 320  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<400> 320  
 Pro Ala Cys His Ser Pro Leu Pro Leu Pro Gly Ser Arg Pro Gly Pro  
           1                  5                  10                  15  
 Asp His Pro Ala Gly Leu Leu Cys Val  
                   20                  25

<210> 321  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 321  
 Ser Gly Cys Arg His Pro Ala Val Cys Gly Gly Ala Gln Met Pro Gly  
           1                  5                  10                  15  
 Asp Gly Arg Ser Thr Ser Asp His Gly Gly  
                   20                  25

<210> 322  
 <211> 95  
 <212> PRT  
 <213> Homo sapiens

<400> 322  
 Gly Leu Lys Val Met Glu Ile Cys Ser Leu Thr Phe Leu Glu Ala Thr  
           1                  5                  10                  15  
 Asn Leu Gln Ser Arg Cys Gln Gln Ala Met Leu Pro Leu Lys Ala Leu  
                   20                  25                  30  
 Arg Lys Asn Pro Phe Leu Leu Leu Pro Ser Phe Asp Gly Cys Cys Gln  
                   35                  40                  45  
 Ser Leu Ala Phe Pro Gly Leu Trp Leu Gln His Ser Asn Leu Cys Leu  
           50                  55                  60  
 Asn His His Met Thr Phe Leu Val Tyr Leu Leu Cys Val Ser Val Phe  
           65                  70                  75                  80  
 Lys Tyr Phe Phe Pro Phe Ser Cys Thr Tyr Thr Ser His Trp Ile  
                   85                  90                  95

<210> 323  
 <211> 22  
 <212> PRT  
 <213> Homo sapiens

<400> 323

**SUBSTITUTE SHEET (RULE 26)**

172

Ile Cys Ser Leu Thr Phe Leu Glu Ala Thr Asn Leu Gln Ser Arg Cys  
 1 5 10 15

Gln Gln Ala Met Leu Pro  
 20

&lt;210&gt; 324

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 324

Gly Leu Trp Leu Gln His Ser Asn Leu Cys Leu Asn His His Met Thr  
 1 5 10 15

Phe Leu Val Tyr Leu Leu Cys Val Ser Val  
 20 25

&lt;210&gt; 325

&lt;211&gt; 37

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 325

Pro Phe Pro Leu Leu Pro Pro Lys Arg Arg Gly Leu Leu Tyr His Leu  
 1 5 10 15

Ile Gln Lys Ser Thr Leu Gly Leu Val Val Trp Phe Arg Glu His Leu  
 20 25 30

Asp Ser Arg Ser Gln  
 35

&lt;210&gt; 326

&lt;211&gt; 78

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (3)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (46)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (48)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

SUBSTITUTE SHEET (RULE 26)

173

&lt;221&gt; SITE

&lt;222&gt; (65)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 326

Arg Gly Xaa Pro Ser Trp Pro Met His Thr Leu Val Tyr Ala Gln His  
 1 5 10 15

Ser Thr Thr His Thr Pro Leu Ile Gln Pro Gln Trp Thr Gln Val Ile  
 20 25 30

Asp Gln Pro Pro Gly Ile Thr His Gln Phe Cys Val Arg Xaa Cys Xaa  
 35 40 45

Cys Pro Thr Leu Glu Ser Cys Val Gln Glu Cys Val Thr Arg Ser Arg  
 50 55 60

Xaa Lys Pro Thr Thr Gly Val Pro Gly Pro Gln Arg Leu Ala  
 65 70 75

&lt;210&gt; 327

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 327

Thr Pro Leu Ile Gln Pro Gln Trp Thr Gln Val Ile Asp Gln Pro Pro  
 1 5 10 15

Gly Ile Thr His Gln Phe Cys Val  
 20

&lt;210&gt; 328

&lt;211&gt; 104

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 328

Ala Leu Gly Pro Ser Gln Thr Cys Asp Leu Asp Val Trp Leu Val Ala  
 1 5 10 15

Lys Pro Ser Phe Phe Arg Gly Pro Gln Gly Ile His Tyr Phe Ser Leu  
 20 25 30

Trp Arg Arg Lys Pro Leu Ser His Trp Val Ser Ile Trp Gln Leu Gln  
 35 40 45

Gly Gln Glu Thr Met Pro Ala Met Leu Arg Ser Arg Pro Ala Gly Gln  
 50 55 60

Ala Thr Val Ala Thr Gly Pro Pro Arg Gly Ser Pro Ser Pro Gln Asp  
 65 70 75 80

Leu Pro Ser Tyr His Arg Lys Gln Val Glu Ser Ser His Arg His Ser  
 85 90 95

SUBSTITUTE SHEET (RULE 26)

Trp Glu Pro Ala Ser Gln Ser Gln  
100

<210> 329  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 329  
Cys Asp Leu Asp Val Trp Leu Val Ala Lys Pro Ser Phe Phe Arg Gly  
1 5 10 15

Pro Gln Gly Ile His Tyr Phe Ser Leu Trp Arg Arg  
20 25

<210> 330  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 330  
Ala Gly Gln Ala Thr Val Ala Thr Gly Pro Pro Arg Gly Ser Pro Ser  
1 5 10 15

Pro Gln Asp Leu Pro Ser Tyr His Arg Lys Gln Val  
20 25

<210> 331  
<211> 79  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (1)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (5)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (15)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 331  
Xaa Gly Asp Thr Xaa Thr Gln Asn Ser Arg His Asp Thr Pro Xaa Leu  
1 5 10 15

Ile Asp Tyr Tyr Arg Glu Ser Cys Thr Leu Gln Tyr Arg Pro Glu Phe  
20 25 30

**SUBSTITUTE SHEET (RULE 26)**



Pro Gly Arg Pro Thr Arg Pro Arg Gly Ser Cys Pro Gln Tyr Pro Gly  
                   35                                  40                                  45

Pro Ala Ile Pro Arg Thr Ser Trp Ala Leu Gly Glu Gly Asp Ala Ala  
                   50                                  55                                  60

Pro Arg Gly Ala His His Pro Arg Arg Ala Asp Val Pro Leu Gly  
                   65                                  70                                  75

<210> 332

<211> 30

<212> PRT

<213> Homo sapiens

<400> 332

Tyr Arg Glu Ser Cys Thr Leu Gln Tyr Arg Pro Glu Phe Pro Gly Arg  
                   1                                  5                                  10                                  15

Pro Thr Arg Pro Arg Gly Ser Cys Pro Gln Tyr Pro Gly Pro  
                   20                                  25                                  30

<210> 333

<211> 155

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (72)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 333

Gly Lys Leu Tyr Ala Ala Val Pro Ser Gly Ile Pro Gly Ser Thr His  
                   1                                  5                                  10                                  15

Ala Ser Ala Arg Leu Met Pro Pro Val Ser Arg Ser Ser Tyr Ser Glu  
                   20                                  25                                  30

Asp Ile Val Gly Ser Arg Arg Arg Arg Arg Ser Ser Ser Gly Ser Pro  
                   35                                  40                                  45

Pro Ser Pro Gln Ser Arg Cys Ser Ser Trp Asp Gly Cys Ser Arg Ser  
                   50                                  55                                  60

His Ser Arg Gly Arg Glu Gly Xaa Arg Pro Pro Trp Ser Glu Leu Asp  
                   65                                  70                                  75                                  80

Val Gly Ala Leu Tyr Pro Phe Ser Arg Ser Gly Ser Arg Gly Arg Leu  
                   85                                  90                                  95

Pro Arg Phe Arg Asn Tyr Ala Phe Ala Ser Ser Trp Ser Thr Ser Tyr  
                   100                                  105                                  110

Ser Gly Tyr Arg Tyr His Arg Ala Leu Leu Cys Arg Arg Thr Ala Val

**SUBSTITUTE SHEET (RULE 26)**

176

115

120

125

Ser Gly Arg Leu Arg Glu Gly Arg Glu Pro Ser Ala Glu Glu Ala Glu  
 130 135 140

Gly Glu Arg Glu Asp Trp Gly Ile Gly Ser Ala  
 145 150 155

&lt;210&gt; 334

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 334

Ser Gly Ile Pro Gly Ser Thr His Ala Ser Ala Arg Leu Met Pro Pro  
 1 5 10 15

Val Ser Arg Ser Ser Tyr Ser  
 20

&lt;210&gt; 335

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (13)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 335

Gly Cys Ser Arg Ser His Ser Arg Gly Arg Glu Gly Xaa Arg Pro Pro  
 1 5 10 15

Trp Ser Glu Leu Asp Val Gly Ala Leu Tyr Pro Phe Ser  
 20 25

&lt;210&gt; 336

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 336

Thr Ala Val Ser Gly Arg Leu Arg Glu Gly Arg Glu Pro Ser Ala Glu  
 1 5 10 15

Glu Ala Glu Gly Glu Arg Glu Asp Trp  
 20 25

&lt;210&gt; 337

&lt;211&gt; 134

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

SUBSTITUTE SHEET (RULE 26)

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (17)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (77)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 337

Arg	Ile	Arg	Lys	Ala	Ala	Val	Gln	Ile	Pro	Thr	Arg	Lys	Asn	Ile	Gly
1				5					10					15	

Xaa	Arg	Arg	Pro	Val	Val	Gln	Glu	Thr	Arg	Lys	Lys	Glu	Arg	Ile	Ser
			20					25					30		

Arg	Leu	Lys	Glu	Ser	Ile	Gly	Asn	Ile	Leu	Ile	Val	Thr	Val	Thr	Gln
		35					40					45			

Ser	Leu	Thr	Gln	Ile	Leu	Thr	Leu	Met	Met	Ile	Lys	Arg	Glu	Leu	Lys
	50					55					60				

Pro	Arg	Arg	Lys	Arg	Arg	Lys	Arg	Asn	Thr	Lys	Gln	Xaa	Lys	Arg	Arg
	65				70					75					80

Ile	Arg	Lys	Pro	Lys	Lys	Asn	Pro	Val	Thr	Gln	Ala	Val	Lys	Thr	Gln
				85					90					95	

Lys	Arg	Thr	Cys	Gln	Lys	Leu	Pro	Gly	Met	Glu	Gln	Pro	Asn	Val	Ala
			100					105					110		

Asp	Thr	Met	Asp	Leu	Ile	Gly	Pro	Glu	Ala	Pro	Ile	Asn	Thr	Tyr	Leu
		115					120					125			

Phe	Lys	Met	Lys	Asn	Leu
	130				

&lt;210&gt; 338

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 338

Thr	Arg	Lys	Lys	Glu	Arg	Ile	Ser	Arg	Leu	Lys	Glu	Ser	Ile	Gly	Asn
1				5					10					15	

Ile	Leu	Ile	Val	Thr	Val	Thr	Gln	Ser	Leu	Thr	Gln
			20				25				

&lt;210&gt; 339

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

SUBSTITUTE SHEET (RULE 26)

&lt;400&gt; 339

Val Lys Thr Gln Lys Arg Thr Cys Gln Lys Leu Pro Gly Met Glu Gln  
 1 5 10 15

Pro Asn Val Ala Asp Thr Met Asp Leu Ile Gly Pro  
 20 25

&lt;210&gt; 340

&lt;211&gt; 80

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 340

Leu Pro Phe Thr Leu Lys Pro Lys Met Val Lys Ile Pro Phe Ser Ser  
 1 5 10 15

Arg Leu Ile Asn Asn Asn Leu Gln Tyr Ile Asp Cys Ile Leu Ser Leu  
 20 25 30

Lys Arg Cys Glu Glu Ile Leu Leu Met Trp His Gly Leu Leu Leu Cys  
 35 40 45

Leu Ala Ser Val Phe Leu Glu Leu Arg Gly Asp Arg Pro Pro Leu Leu  
 50 55 60

Ala Ser Leu Leu Glu Pro His Lys Met Pro Leu His Ser Ser Ser Leu  
 65 70 75 80

&lt;210&gt; 341

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 341

Leu Lys Pro Lys Met Val Lys Ile Pro Phe Ser Ser Arg Leu Ile Asn  
 1 5 10 15

Asn Asn Leu Gln Tyr Ile Asp Cys  
 20

&lt;210&gt; 342

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 342

Ser Leu Lys Arg Cys Glu Glu Ile Leu Leu Met Trp His Gly Leu Leu  
 1 5 10 15

Leu Cys Leu Ala Ser Val Phe

SUBSTITUTE SHEET (RULE 26)

20

<210> 343  
 <211> 21  
 <212> PRT  
 <213> Homo sapiens

<400> 343  
 Leu Arg Gly Asp Arg Pro Pro Leu Leu Ala Ser Leu Leu Glu Pro His  
           1                          5                          10                          15  
 Lys Met Pro Leu His  
                           20

<210> 344  
 <211> 79  
 <212> PRT  
 <213> Homo sapiens

<400> 344  
 Leu Gln Met His Thr Gly Ser Gly Phe Lys Gly Lys Ser Cys Glu Val  
           1                          5                          10                          15  
 Ala Phe Tyr Val Ala Gln Ala Glu Lys Pro Gly Glu Gly Ala Tyr Leu  
                           20                          25                          30  
 His Gly Ala Gln Glu Thr Gln Lys Gln Gly Ile Glu Ala Asp His Ala  
           35                          40                          45  
 Thr Leu Arg Gly Ser Pro His Ser Val Ser Lys Thr Lys Tyr Asn Leu  
           50                          55                          60  
 Tyr Ile Ala Asn Tyr Tyr Leu Leu Ala Trp Arg Lys Met Glu Ser  
           65                          70                          75

<210> 345  
 <211> 20  
 <212> PRT  
 <213> Homo sapiens

<400> 345  
 Cys Glu Val Ala Phe Tyr Val Ala Gln Ala Glu Lys Pro Gly Glu Gly  
           1                          5                          10                          15  
 Ala Tyr Leu His  
                           20

<210> 346  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 346

SUBSTITUTE SHEET (RULE 26)

180

Ala Thr Leu Arg Gly Ser Pro His Ser Val Ser Lys Thr Lys Tyr Asn  
 1 5 10 15

Leu Tyr Ile Ala Asn Tyr Tyr  
 20

&lt;210&gt; 347

&lt;211&gt; 65

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 347

Leu Ser Ala Ser Leu Leu Asp Arg Tyr Pro Ala Ser Glu Ser Asn Asn  
 1 5 10 15

Tyr Ile Phe Asn Phe Val Leu Tyr Met Leu His Phe Leu Ala Gly Thr  
 20 25 30

Leu Phe Ser Leu Phe Pro Asp Phe Glu Leu Ser Pro Arg Ser Ala Thr  
 35 40 45

Leu Phe Pro Asp Leu Arg Thr Val Gln Leu Leu Ser Ser Arg Pro His  
 50 55 60

Leu

65

&lt;210&gt; 348

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 348

Leu Leu Asp Arg Tyr Pro Ala Ser Glu Ser Asn Asn Tyr Ile Phe Asn  
 1 5 10 15

Phe Val Leu Tyr Met Leu His  
 20

&lt;210&gt; 349

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 349

Phe Pro Asp Phe Glu Leu Ser Pro Arg Ser Ala Thr Leu Phe Pro Asp  
 1 5 10 15

Leu Arg Thr Val  
 20

&lt;210&gt; 350

&lt;211&gt; 85

SUBSTITUTE SHEET (RULE 26)

181

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 350

Asn Gly Gly Phe Tyr Asp Val Ser Phe Lys Gln Ala Gly Leu Ile Glu  
 1 5 10 15

Phe Leu Cys Ile Ile Tyr Phe Tyr Pro Met Ala His Val Ile Cys Gly  
 20 25 30

Ser Arg Phe Thr Ile Val Arg Thr Ile Pro Val His Tyr Val Gly Glu  
 35 40 45

Tyr Phe Ile Lys Ser Ser Ile Trp Ile Leu Tyr Arg Ile Asn Glu Arg  
 50 55 60

Thr Ala Thr Lys Lys Ala Ala Ser Asp Phe Gln Lys Asn Phe Arg Cys  
 65 70 75 80

Phe Leu Asp Ala Phe  
 85

&lt;210&gt; 351

&lt;211&gt; 19

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 351

Lys Gln Ala Gly Leu Ile Glu Phe Leu Cys Ile Ile Tyr Phe Tyr Pro  
 1 5 10 15

Met Ala His

&lt;210&gt; 352

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 352

Tyr Phe Ile Lys Ser Ser Ile Trp Ile Leu Tyr Arg Ile Asn Glu Arg  
 1 5 10 15

Thr Ala Thr Lys Lys Ala Ala  
 20

&lt;210&gt; 353

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (4)

SUBSTITUTE SHEET (RULE 26)

182

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (7)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (9)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 353

Ser	Pro	Arg	Xaa	Gly	Arg	Xaa	Phe	Xaa	Thr	Ser	Arg	Lys	Gln	Ile	Ser
1				5					10					15	

Gly	Phe	Leu	Glu	Phe	Asp
					20

&lt;210&gt; 354

&lt;211&gt; 56

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 354

Met	Lys	His	Ala	Ala	Phe	Gly	Leu	Ile	Pro	Leu	Val	Lys	Glu	Ile	Tyr
1				5					10					15	

Arg	Tyr	Leu	Lys	Ile	Lys	Ser	Lys	Leu	Leu	Ile	Gly	Ser	Gly	Lys	Cys
			20					25						30	

Gln	Leu	Gln	Pro	Glu	Trp	Leu	Gln	Thr	Ser	Leu	Ile	Asn	Ser	Ser	Leu
		35					40					45			

Leu	Met	Asp	Trp	Leu	Thr	Pro	Tyr
	50					55	

&lt;210&gt; 355

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 355

Ile	Tyr	Arg	Tyr	Leu	Lys	Ile	Lys	Ser	Lys	Leu	Leu	Ile	Gly	Ser	Gly
1				5					10					15	

Lys	Cys	Gln	Leu	Gln	Pro	Glu	Trp	Leu	Gln	Thr	Ser	Leu
			20					25				

&lt;210&gt; 356

&lt;211&gt; 68

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

SUBSTITUTE SHEET (RULE 26)



183

&lt;400&gt; 356

Gln Leu Gly Leu Pro Trp Asp Gln Ser Lys Gly Pro Arg Lys Asn Gly  
1 5 10 15

Leu Ser Met Cys Gly Ser Val Tyr Ser Thr Ile Trp Ser Leu Ile Ala  
20 25 30

Ser Arg Arg Glu Glu Thr Ile Arg Val Ile Val Leu Tyr Ile Gln Ser  
35 40 45

Pro Asn Ile Asn Thr Arg His Ile Ser Lys Arg Gly Leu Asn Lys Ala  
50 55 60

Leu Thr Asn Pro  
65

&lt;210&gt; 357

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 357

Ser Lys Gly Pro Arg Lys Asn Gly Leu Ser Met Cys Gly Ser Val Tyr  
1 5 10 15

Ser Thr Ile Trp Ser  
20

&lt;210&gt; 358

&lt;211&gt; 17

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 358

Gln Ser Pro Asn Ile Asn Thr Arg His Ile Ser Lys Arg Gly Leu Asn  
1 5 10 15

Lys

&lt;210&gt; 359

&lt;211&gt; 19

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 359

His Pro Gln Thr Ser Ala Gly Gly Phe Pro Leu His Gln Gly Leu Pro  
1 5 10 15

Thr Val Ser

&lt;210&gt; 360

SUBSTITUTE SHEET (RULE 26)

&lt;211&gt; 117

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (110)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 360

Pro Ser Trp Phe Pro Glu Leu Ser Pro Trp Pro Leu Lys Thr Leu Lys  
 1 5 10 15

Lys Arg Arg Gln Met Arg Leu Arg Arg Arg Gly Arg Leu Cys Arg Leu  
 20 25 30

Ser Pro Ala Thr Thr Thr Thr Ala Asp Thr Cys Arg Cys Pro Ala Arg  
 35 40 45

Ser Tyr Arg Gly Ser Gly Arg Arg Pro Ala Cys Ala Gln Asp Ser Pro  
 50 55 60

Ala Pro Pro Ser Arg Pro Thr Arg Arg Ala Trp Glu Lys Cys Ala Leu  
 65 70 75 80

Arg Pro Lys Arg Ala Ala Gln Trp Ser Thr Gly Val Pro Pro Ser Pro  
 85 90 95

Arg Ser Ser Thr Thr Gly Cys Cys Phe Gly Thr Ala Ala Xaa Cys Ala  
 100 105 110

Glu Gly Ala Arg Arg  
 115

&lt;210&gt; 361

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 361

Thr Thr Thr Ala Asp Thr Cys Arg Cys Pro Ala Arg Ser Tyr Arg Gly  
 1 5 10 15

Ser Gly Arg Arg Pro Ala  
 20

&lt;210&gt; 362

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 362

Pro Ser Arg Pro Thr Arg Arg Ala Trp Glu Lys Cys Ala Leu Arg Pro  
 1 5 10 15

185

Lys Arg Ala Ala Gln Trp Ser Thr  
20

<210> 363  
<211> 20  
<212> PRT  
<213> Homo sapiens

<400> 363  
Ala Arg Gly Val Leu Asn Leu Arg Asn Arg Phe Glu Cys Phe Ser Ile  
1 5 10 15

Ile Glu Thr Val  
20

<210> 364  
<211> 69  
<212> PRT  
<213> Homo sapiens

<400> 364  
Ile Gly Gln Leu Val Met Lys Ser Ile Cys His Phe Gln Arg Leu Leu  
1 5 10 15

Ser Val Ala Ile Asp Phe Ala Ser Gln Phe Leu Lys Asn Tyr Ile Phe  
20 25 30

Ser Ser Thr His Ser Ser Lys Ala Gly Phe Ser Val Val Cys Ser Leu  
35 40 45

Pro Lys Trp Leu Tyr Thr Asp Gly Met Glu Met Val Leu Lys Ile Thr  
50 55 60

His Lys Leu Ser Phe  
65

<210> 365  
<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 365  
Gln Arg Leu Leu Ser Val Ala Ile Asp Phe Ala Ser Gln Phe Leu Lys  
1 5 10 15

Asn Tyr Ile Phe Ser Ser Thr His  
20

<210> 366  
<211> 12  
<212> PRT  
<213> Homo sapiens

SUBSTITUTE SHEET (RULE 26)

186

&lt;400&gt; 366

Leu Met Lys Thr Ala Ser Arg Met Leu Leu Leu Glu  
 1 5 10

&lt;210&gt; 367

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (3)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (6)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 367

Ala Thr Xaa Trp Asp Xaa Pro Gly Cys Arg Asn Ser Ala Arg Gly Glu  
 1 5 10 15

Arg Leu His Val Gly Asp Ala Pro Trp  
 20 25

&lt;210&gt; 368

&lt;211&gt; 109

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (102)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (105)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 368

Ala Arg Asp Glu Arg Arg Glu Val Leu Lys Thr Leu Met Arg Leu Ser  
 1 5 10 15

Thr Gln Arg Pro Gln Ala Phe Leu Pro Ser Gln Ser Trp Phe Val Arg  
 20 25 30

Leu Gln Lys Ala Gly Glu Gly Ala Leu Lys Gln Glu Asn Ser Leu Thr  
 35 40 45

Ile Gln Asn Cys Leu Leu Cys Leu Pro Arg Val His Arg Gln Arg Pro  
 50 55 60

Thr Pro Pro Gln Pro Gln Arg Gly Asn Thr Glu Ala Ser Val Leu Gln

SUBSTITUTE SHEET (RULE 26)

```
<400> 372
Ala Leu Val Ile Ser Asn Pro Leu Leu
  1             5
```

&lt;210&gt; 373

&lt;211&gt; 63

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 373

Pro Tyr Ile Asn Thr Gln Met Cys Val Ser Ser Arg Asn Lys Phe Cys  
1 5 10 15

Ile Ser Gly His Gln Lys Tyr Asp Ser His Gly Arg Glu Thr Arg Phe  
20 25 30

Glu Met His Lys Ala Arg Ala Ser Ser Trp Lys Asn Ile Leu Lys Ile  
35 40 45

Arg Ser Leu Lys Ile Ile Ser Arg Gly Phe Glu Ile Thr Asn Ala  
50 55 60

&lt;210&gt; 374

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 374

Lys Phe Cys Ile Ser Gly His Gln Lys Tyr Asp Ser His Gly Arg Glu  
1 5 10 15

Thr Arg Phe Glu Met His Lys Ala Arg Ala Ser  
20 25

&lt;210&gt; 375

&lt;211&gt; 84

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 375

His Thr Leu Leu Glu Ile Ala Asn Pro Leu Gln Ala Ala Val Leu Gly  
1 5 10 15

Ala Ser Ser Ile His Pro Ser Ile His Thr Ser Thr His Leu Met Phe  
20 25 30

Met Gly Leu Lys Trp Thr Glu Leu His His Ser Pro Asp Ser Val Gln  
35 40 45

Gly Ala Gly Ala Ala Glu Ala Ala Gln Thr Arg His Ser Leu Arg Pro  
50 55 60

Gly Arg Gly Arg Glu Arg His Asp Cys Thr Leu Lys Asn Leu Thr Leu  
65 70 75 80

Phe Ile Ile Cys

SUBSTITUTE SHEET (RULE 26)

<210> 376  
 <211> 22  
 <212> PRT  
 <213> Homo sapiens

<400> 376  
 Asn Pro Leu Gln Ala Ala Val Leu Gly Ala Ser Ser Ile His Pro Ser  
 1 5 10 15  
 Ile His Thr Ser Thr His  
 20

<210> 377  
 <211> 17  
 <212> PRT  
 <213> Homo sapiens

<400> 377  
 Ser Leu Arg Pro Gly Arg Gly Arg Glu Arg His Asp Cys Thr Leu Lys  
 1 5 10 15

Asn

<210> 378  
 <211> 52  
 <212> PRT  
 <213> Homo sapiens

<400> 378  
 Ala Glu Asn Val His Cys Thr Pro Ala Trp Glu Thr Gly Arg Asp Ser  
 1 5 10 15

Glu Asp Gly Lys Gly Arg Glu Gly Met Gly Arg Asp Arg Lys Gly Trp  
 20 25 30

Asp Gly Thr Gly Leu Asp Gly Thr Gly Trp Glu Gly Lys Arg Glu Arg  
 35 40 45

Asn Val Pro Ala  
 50

<210> 379  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 379  
 Gly Arg Asp Ser Glu Asp Gly Lys Gly Arg Glu Gly Met Gly Arg Asp  
 1 5 10 15

Arg Lys Gly Trp Asp Gly Thr Gly Leu Asp  
 20 25

**SUBSTITUTE SHEET (RULE 26)**

&lt;210&gt; 380

&lt;211&gt; 14

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 380

Thr Ser Leu Gly Asp Leu Trp Asp Tyr Asn Asn Ser Ser His  
 1 5 10

&lt;210&gt; 381

&lt;211&gt; 66

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 381

Asp Arg Arg Ile Ile Arg Thr Arg Glu Ala Ala Val Ala Val Ser Arg  
 1 5 10 15

Glu Arg Pro Leu His Ser Ser Leu Gly Asn Arg Glu Arg Leu Arg Arg  
 20 25 30

Trp Glu Gly Thr Gly Arg Asp Gly Lys Gly Gln Glu Gly Met Gly Arg  
 35 40 45

Asp Gly Thr Gly Trp Asp Gly Met Gly Arg Glu Glu Arg Lys Lys Cys  
 50 55 60

Pro Ser  
 65

&lt;210&gt; 382

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 382

Arg Pro Leu His Ser Ser Leu Gly Asn Arg Glu Arg Leu Arg Arg Trp  
 1 5 10 15

Glu Gly Thr Gly Arg Asp Gly Lys Gly  
 20 25

&lt;210&gt; 383

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 383

Asn Gln Ser Trp Gly Pro Met Gly Leu  
 1 5

SUBSTITUTE SHEET (RULE 26)



<210> 384  
 <211> 59  
 <212> PRT  
 <213> Homo sapiens

<400> 384  
 Gly Gly Gly Gly Cys Ser Glu Pro Arg Thr Ser Ile Ala Leu Gln Pro  
           1                  5                  10                  15  
 Gly Lys Gln Gly Glu Thr Pro Lys Met Gly Arg Asp Gly Lys Gly Trp  
                   20                  25                  30  
 Glu Gly Thr Gly Arg Asp Gly Thr Gly Arg Asp Trp Met Gly Arg Asp  
           35                  40                  45  
 Gly Lys Gly Arg Glu Lys Glu Met Ser Gln Gln  
           50                  55

<210> 385  
 <211> 24  
 <212> PRT  
 <213> Homo sapiens

<400> 385  
 Lys Gln Gly Glu Thr Pro Lys Met Gly Arg Asp Gly Lys Gly Trp Glu  
           1                  5                  10                  15  
 Gly Thr Gly Arg Asp Gly Thr Gly  
           20

<210> 386  
 <211> 32  
 <212> PRT  
 <213> Homo sapiens

<400> 386  
 Pro Val Leu Gly Thr Tyr Gly Thr Ile Thr Thr Pro Val Thr Glu Leu  
           1                  5                  10                  15  
 Thr Lys Gly Gln Glu Lys Glu Gly Gly Val Glu Thr Val Leu Tyr Glu  
           20                  25                  30

<210> 387  
 <211> 11  
 <212> PRT  
 <213> Homo sapiens

<400> 387  
 Lys Ile Val Phe Ile Asp Gln Lys Trp Ser Lys  
           1                  5                  10

**SUBSTITUTE SHEET (RULE 26)**

&lt;210&gt; 388

&lt;211&gt; 70

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 388

Cys Ser Leu Phe Trp Gly Ile Leu Phe Leu Ser Arg Leu Arg Ile His

1

5

10

15

Leu Phe Leu Ser Leu Lys Pro Cys Met Cys Leu Arg Pro Ile Asp Ile

20

25

30

Leu Ser His Phe Leu Asp Ile Phe Val Thr Ser Val Leu Ser Glu Leu

35

40

45

Glu Lys Ser Ser Leu Lys Thr Thr Glu Thr Phe Ser Phe Ala Val Phe

50

55

60

Leu Leu Leu Met Met Asn

65

70

&lt;210&gt; 389

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 389

Leu Ser Arg Leu Arg Ile His Leu Phe Leu Ser Leu Lys Pro Cys Met

1

5

10

15

Cys Leu Arg Pro Ile Asp Ile Leu Ser His

20

25

&lt;210&gt; 390

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 390

Val Leu Ser Glu Leu Glu Lys Ser Ser Leu Lys Thr Thr Glu Thr Phe

1

5

10

15

Ser Phe Ala Val Phe Leu

20

&lt;210&gt; 391

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 391

Thr Leu Phe Arg Tyr Ile Leu His

1

5

SUBSTITUTE SHEET (RULE 26)

<210> 392  
 <211> 14  
 <212> PRT  
 <213> Homo sapiens

<400> 392  
 Gly Thr Ser Phe Ser Val Leu Ser Leu Ile His Asp Thr Gly  
           1                          5                          10

<210> 393  
 <211> 63  
 <212> PRT  
 <213> Homo sapiens

<400> 393  
 Val Leu Ile Ser Ala Ser Thr Ile Gly Ser Arg Thr Ser Gly Ala Gln  
           1                          5                          10                          15  
  
 Gly Met Glu Lys Met Thr Ile Pro Thr Leu Ala Val Gly Glu Pro Lys  
                           20                          25                          30  
  
 Thr Pro Glu Lys Ser Lys Cys Ser Leu Lys Gln Cys Phe Ser Ser Cys  
                           35                          40                          45  
  
 Asn Val His Ile Asp His Leu Gly Leu Leu Leu Lys Cys Lys Phe  
           50                          55                          60

<210> 394  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 394  
 Ala Ser Thr Ile Gly Ser Arg Thr Ser Gly Ala Gln Gly Met Glu Lys  
           1                          5                          10                          15  
  
 Met Thr Ile Pro Thr Leu Ala  
                           20

<210> 395  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 395  
 Gly Glu Pro Lys Thr Pro Glu Lys Ser Lys Cys Ser Leu Lys Gln Cys  
           1                          5                          10                          15  
  
 Phe Ser Ser Cys Asn Val His Ile Asp His Leu  
                           20                          25

194

&lt;210&gt; 396

&lt;211&gt; 101

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 396

Arg Ile Arg Ser Gln Asp Leu Ala Ile Met Thr Thr Cys Phe Lys Lys  
 1 5 10 15

Tyr Glu Phe Ser Phe Phe Val Leu Gly Phe Leu Arg Arg Trp Gly Ala  
 20 25 30

Thr Leu Cys Leu Gly Phe Thr Ser Phe Ala Ile Lys Phe His Pro Ser  
 35 40 45

Ser Leu Cys Ser Glu Lys Glu Gly Lys Asp Phe Ser Gly Phe Ala Leu  
 50 55 60

Ser Ile His Gly Pro Glu Arg Lys Lys Glu Glu Gly Trp Ala Arg Trp  
 65 70 75 80

Leu Thr Pro Val Val Pro Val Leu Trp Glu Ala Glu Val Gly Gly Ser  
 85 90 95

Pro Glu Val Ser Ser  
 100

&lt;210&gt; 397

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 397

Thr Thr Cys Phe Lys Lys Tyr Glu Phe Ser Phe Phe Val Leu Gly Phe  
 1 5 10 15

Leu Arg Arg Trp Gly Ala  
 20

&lt;210&gt; 398

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 398

Ser Glu Lys Glu Gly Lys Asp Phe Ser Gly Phe Ala Leu Ser Ile His  
 1 5 10 15

Gly Pro Glu Arg Lys Lys Glu Glu Gly Trp  
 20 25

&lt;210&gt; 399

&lt;211&gt; 86

&lt;212&gt; PRT

SUBSTITUTE SHEET (RULE 26)

195

&lt;213&gt; Homo sapiens

&lt;400&gt; 399

```

Met Asn Glu Cys Ile Ala Lys Pro Cys Met Ala Ala Phe Cys Ser Cys
 1             5             10             15

Pro Ser Cys Cys Leu Pro Ser Arg Pro Gly Cys Ser Arg Glu Gln Arg
          20             25             30

Cys Ala Phe Ser Cys Glu Pro Cys His Thr Val Glu His Trp Val Glu
          35             40             45

Pro Met Gly Gln Gly Gln Arg Gln Glu His Thr Gln Gly Ser Val Leu
          50             55             60

Pro Ser Ser His Pro Ser Arg Gly Lys Ala Thr Thr Val His Ser Cys
          65             70             75             80

Cys Gln Glu Pro Trp Gly
          85

```

&lt;210&gt; 400

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 400

```

Phe Cys Ser Cys Pro Ser Cys Cys Leu Pro Ser Arg Pro Gly Cys Ser
 1             5             10             15

Arg Glu Gln Arg Cys Ala Phe Ser Cys Glu Pro
          20             25

```

&lt;210&gt; 401

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 401

```

Gly Gln Arg Gln Glu His Thr Gln Gly Ser Val Leu Pro Ser Ser His
 1             5             10             15

Pro Ser Arg Gly Lys Ala Thr
          20

```

&lt;210&gt; 402

&lt;211&gt; 139

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 402

```

Gly Val Val Asn Ser Cys Leu Leu Pro Leu Pro Pro Arg Leu Leu Ala
 1             5             10             15

```

SUBSTITUTE SHEET (RULE 26)

196

Thr Gly Met Asp Cys Gly Gly Phe Ala Ser Arg Arg Met Gly Gly Arg  
                   20                  25                  30

Gln His Ala Ala Leu Ser Val Phe Leu Pro Leu Pro Leu Ala His Gly  
                   35                  40                  45

Leu Tyr Pro Met Phe Asn Cys Val Ala Gly Leu Thr Gly Lys Gly Thr  
                   50                  55                  60

Ser Leu Leu Ser Gly Ala Ala Arg Pro Ala Gly Glu Ala Ala Ala Arg  
                   65                  70                  75                  80

Ala Gly Thr Lys Gly Ser His Ala Arg Phe Gly Asn Ala Phe Ile His  
                   85                  90                  95

Ser Phe Ile His Ser Phe Ile Glu Cys Leu Leu Asn Thr Tyr Cys Val  
                   100                  105                  110

Pro Ser Ser Ala Leu Thr Ala Val Gly Ile Gly Asp Ile Leu Lys Asn  
                   115                  120                  125

Lys Asn Asp Lys Ser Ser Cys Leu Cys Ser Cys  
                   130                  135

&lt;210&gt; 403

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 403

Gly Met Asp Cys Gly Gly Phe Ala Ser Arg Arg Met Gly Gly Arg Gln  
                   1                  5                  10                  15

His Ala Ala Leu Ser Val Phe Leu Pro  
                   20                  25

&lt;210&gt; 404

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 404

Leu Thr Gly Lys Gly Thr Ser Leu Leu Ser Gly Ala Ala Arg Pro Ala  
                   1                  5                  10                  15

Gly Glu Ala Ala Ala Arg Ala Gly Thr  
                   20                  25

&lt;210&gt; 405

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 405

SUBSTITUTE SHEET (RULE 26)

197

Leu Asn Thr Tyr Cys Val Pro Ser Ser Ala Leu Thr Ala Val Gly Ile  
 1 5 10 15

Gly Asp Ile Leu Lys Asn  
 20

&lt;210&gt; 406

&lt;211&gt; 55

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 406

Thr Ser Leu Ser Gln Leu Trp His Phe Cys His Phe Trp Pro Val Lys  
 1 5 10 15

Phe Cys Cys Gly Gly Cys Pro Val His Cys Arg Met Phe Ser Ser Ile  
 20 25 30

Ser Gly Leu Tyr Leu Leu Asn Ala Ser Ala Pro Ser Leu Gln Leu Asn  
 35 40 45

Asp Pro Lys Cys Leu Gln Thr  
 50 55

&lt;210&gt; 407

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 407

Trp Pro Val Lys Phe Cys Cys Gly Gly Cys Pro Val His Cys Arg Met  
 1 5 10 15

Phe Ser Ser Ile Ser Gly Leu Tyr Leu Leu Asn Ala  
 20 25

&lt;210&gt; 408

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 408

Ser Cys Arg Cys Trp Ala Leu Gly Ala Gly Gly Gly Gln Arg Gln Trp  
 1 5 10 15

Val Gly Arg Ser  
 20

&lt;210&gt; 409

&lt;211&gt; 80

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

SUBSTITUTE SHEET (RULE 26)

198

&lt;400&gt; 409

Thr Gly Ala Gln Ala Pro Lys Met Gly Ala Arg Gln Arg Lys Arg Pro  
 1 5 10 15

Leu Gln Thr Arg Ile Lys Asn Ser Ser Lys Ser Thr Leu Trp Pro Pro  
 20 25 30

Gln Trp Val Arg Cys Gly Arg Trp Trp Thr Trp Pro Ser Arg Lys Lys  
 35 40 45

Thr Ser Arg Pro Arg Arg Gln Leu Phe Thr Ser Thr Leu Ser Thr Ser  
 50 55 60

Ala Ser Ala Leu Val Trp Pro Val Ser Trp Phe Ser Gln Glu Gly His  
 65 70 75 80

&lt;210&gt; 410

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 410

Met Gly Ala Arg Gln Arg Lys Arg Pro Leu Gln Thr Arg Ile Lys Asn  
 1 5 10 15

Ser Ser Lys Ser Thr Leu Trp Pro Pro  
 20 25

&lt;210&gt; 411

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 411

Pro Arg Arg Gln Leu Phe Thr Ser Thr Leu Ser Thr Ser Ala Ser Ala  
 1 5 10 15

Leu Val Trp Pro Val Ser Trp  
 20

&lt;210&gt; 412

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 412

Asp Gly Gly Gly Lys Glu Glu Gly Val Ser Cys Leu Lys Ile Ser Leu  
 1 5 10 15

Leu Cys Gly Pro Trp Leu Trp Leu Pro  
 20 25

SUBSTITUTE SHEET (RULE 26)



<210> 413  
 <211> 135  
 <212> PRT  
 <213> Homo sapiens

<400> 413  
 His Glu Met Gly Glu Leu Ala Ile Cys His Thr Arg Val Pro Phe Ser  
     1                    5                    10                    15  
 Leu Pro Ser Ser Ala Gln Gly Val Pro Gln Asn Leu Gln Gly Pro Ile  
                     20                    25                    30  
 Gly His Leu Ala Val Cys Thr Pro Ser Ser Leu Thr Ser Trp His Phe  
             35                    40                    45  
 Pro Gln Lys Arg Glu Lys Trp Ser Thr Val Asn Lys Arg Gln Arg Phe  
             50                    55                    60  
 Leu Gln Phe Pro Ala Pro Leu Arg Asn Trp Ile Pro Gln Thr Pro Leu  
     65                    70                    75                    80  
 Ser Leu Ser Val Ser Ser Gly Pro Leu Gly Ser Phe Thr Val Phe Thr  
                     85                    90                    95  
 Leu Leu Ser Leu Cys Ala Trp Pro Trp Cys Cys Arg Asp Cys Tyr Lys  
             100                    105                    110  
 Ser Cys Cys Pro Ile Pro Ile Phe Asn Leu Thr Ala Pro Leu Cys Val  
             115                    120                    125  
 His Thr Pro Glu Pro Ser Ser  
     130                    135

<210> 414  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 414  
 Ser Ser Ala Gln Gly Val Pro Gln Asn Leu Gln Gly Pro Ile Gly His  
     1                    5                    10                    15  
 Leu Ala Val Cys Thr Pro Ser  
             20

<210> 415  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 415  
 Val Asn Lys Arg Gln Arg Phe Leu Gln Phe Pro Ala Pro Leu Arg Asn  
     1                    5                    10                    15

200

Trp Ile Pro Gln Thr Pro Leu Ser Leu Ser Val Ser  
                   20                  25

<210> 416  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 416  
 Cys Cys Arg Asp Cys Tyr Lys Ser Cys Cys Pro Ile Pro Ile Phe Asn  
   1                  5                  10                  15

Leu Thr Ala Pro Leu Cys Val  
                   20

<210> 417  
 <211> 150  
 <212> PRT  
 <213> Homo sapiens

<400> 417  
 Asp Leu Asn Val Thr Asn Glu Gly Glu Gly Lys Glu Val Leu Gly Gln  
   1                  5                  10                  15

Gly Ser Thr Asn Asn Glu Lys Lys Cys Gln Lys Ala Thr Ser Asn Thr  
                   20                  25                  30

Glu Pro Arg Ala Arg Glu Ala Lys Ala Arg His Ala Asn Met Gly Thr  
                   35                  40                  45

Ser Asp Arg Glu Ser Pro Thr Trp Ser Leu Thr Ala Glu Gly Leu Lys  
                   50                  55                  60

Ala Lys Ser Lys Met Gln Gly Lys Ala Thr Lys Gly Ala Ala Ser Thr  
   65                  70                  75                  80

Met Gly Ser His Asn Gln Gly Pro His Lys Arg Glu Ile Phe Lys His  
                   85                  90                  95

Glu Thr Pro Ser Ser Phe Pro Pro Pro Ser Gln Cys Gln Pro Glu Leu  
                   100                  105                  110

Leu Pro Tyr Lys Tyr Trp Ala Thr Leu Ala Ser Gly Tyr Val Pro Ser  
                   115                  120                  125

Trp Leu Pro Ser Val Asp Ser Tyr Arg Ile Asn Thr Ala Ile Lys Asp  
                   130                  135                  140

Lys Asn Gly Gln Asp Thr  
   145                  150

<210> 418  
 <211> 24

SUBSTITUTE SHEET (RULE 26)

201

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 418

Val Leu Gly Gln Gly Ser Thr Asn Asn Glu Lys Lys Cys Gln Lys Ala  
1 5 10 15

Thr Ser Asn Thr Glu Pro Arg Ala  
20

&lt;210&gt; 419

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 419

Arg Glu Ser Pro Thr Trp Ser Leu Thr Ala Glu Gly Leu Lys Ala Lys  
1 5 10 15

Ser Lys Met Gln Gly Lys Ala Thr Lys Gly Ala Ala Ser  
20 25

&lt;210&gt; 420

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 420

Gly Tyr Val Pro Ser Trp Leu Pro Ser Val Asp Ser Tyr Arg Ile Asn  
1 5 10 15

Thr Ala Ile Lys Asp Lys  
20

&lt;210&gt; 421

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 421

Asn Ser Ala Glu Gln Ser Met Leu Ile Leu Val Thr  
1 5 10

&lt;210&gt; 422

&lt;211&gt; 122

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

SUBSTITUTE SHEET (RULE 26)

202

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (5)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 422

Arg Xaa Asp Arg Xaa Pro Val Pro Glu Leu Pro Gly Tyr Glu Pro Thr  
 1 5 10 15

Arg Thr Asp Ile Ser Ser Phe Lys Asn Ile Tyr Arg Tyr Ala Phe Asp  
 20 25 30

Phe Ala Arg Asp Lys Asp Gln Arg Ser Leu Asp Ile Asp Thr Ala Lys  
 35 40 45

Ser Met Leu Ala Leu Leu Leu Gly Arg Thr Trp Pro Leu Phe Ser Val  
 50 55 60

Phe Tyr Gln Tyr Leu Glu Gln Ser Lys Tyr Arg Val Met Asn Lys Asp  
 65 70 75 80

Gln Trp Tyr Asn Val Leu Glu Phe Ser Arg Thr Val His Ala Asp Leu  
 85 90 95

Ser Asn Tyr Asp Glu Asp Gly Ala Trp Pro Val Leu Leu Asp Glu Phe  
 100 105 110

Val Glu Trp Gln Lys Val Arg Gln Thr Ser  
 115 120

&lt;210&gt; 423

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 423

Pro Thr Arg Thr Asp Ile Ser Ser Phe Lys Asn Ile Tyr Arg Tyr Ala  
 1 5 10 15

Phe Asp Phe Ala Arg Asp Lys Asp Gln Arg Ser Leu  
 20 25

&lt;210&gt; 424

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 424

Ser Met Leu Ala Leu Leu Leu Gly Arg Thr Trp Pro Leu Phe Ser Val  
 1 5 10 15

Phe Tyr Gln Tyr Leu Glu Gln Ser Lys Tyr Arg Val Met  
 20 25

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203

&lt;210&gt; 425

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 425

Phe Ser Arg Thr Val His Ala Asp Leu Ser Asn Tyr Asp Glu Asp Gly  
1 5 10 15

Ala Trp Pro Val Leu Leu Asp Glu Phe Val Glu  
20 25

&lt;210&gt; 426

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 426

Ile Tyr Arg Tyr Ala Phe Asp Phe Ala Arg  
1 5 10

&lt;210&gt; 427

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 427

Lys Asp Gln Arg Ser Leu Asp Ile  
1 5

&lt;210&gt; 428

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 428

Asn Val Leu Glu Phe Ser Arg Thr  
1 5

&lt;210&gt; 429

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 429

Asp Leu Ser Asn Tyr Asp Glu Asp Gly Ala Trp Pro Val Leu Leu Asp  
1 5 10 15

Glu Phe Val Glu Trp  
20

&lt;210&gt; 430

SUBSTITUTE SHEET (RULE 26)

<211> 37  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (15)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 430  
 Leu Phe Arg Cys Pro Ile Gly Lys Ala Gly Thr Pro Ala Gly Xaa Gly  
           1                          5                          10                          15

Pro Glu Phe Pro Gly Arg Pro Thr Arg Pro Val Arg Glu Lys Glu Leu  
                           20                          25                          30

Thr Glu Thr Phe Glu  
                           35

<210> 431  
 <211> 21  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (9)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 431  
 Gly Lys Ala Gly Thr Pro Ala Gly Xaa Gly Pro Glu Phe Pro Gly Arg  
           1                          5                          10                          15

Pro Thr Arg Pro Val  
                           20

<210> 432  
 <211> 45  
 <212> PRT  
 <213> Homo sapiens

<400> 432  
 Phe Phe Val Phe Pro Tyr Pro Tyr Pro Phe Arg Pro Leu Pro Pro Ile  
           1                          5                          10                          15

Pro Phe Pro Arg Phe Pro Trp Phe Arg Arg Asn Phe Pro Ile Pro Ile  
                           20                          25                          30

Pro Glu Ser Ala Pro Thr Thr Pro Leu Pro Ser Glu Lys  
           35                          40                          45

<210> 433  
 <211> 21  
 <212> PRT

SUBSTITUTE SHEET (RULE 26)

205

&lt;213&gt; Homo sapiens

&lt;400&gt; 433

Pro Trp Phe Arg Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro  
 1 5 10 15

Thr Thr Pro Leu Pro  
 20

&lt;210&gt; 434

&lt;211&gt; 61

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 434

Phe Tyr Pro Pro Met Thr Gln Gly Lys Glu Ser Leu Pro Leu Leu Ala  
 1 5 10 15

Leu Gln Ile Phe Asn Thr Thr Phe Arg Pro Ser Phe Ala Phe Phe Ser  
 20 25 30

Gly His Arg Thr Leu Phe Phe Gly Val Arg Ser Pro Asn Pro Pro Lys  
 35 40 45

Pro Arg Ile Phe Leu Ile Trp Leu Ile Ala Val Ala Leu  
 50 55 60

&lt;210&gt; 435

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 435

Leu Leu Ala Leu Gln Ile Phe Asn Thr Thr Phe Arg Pro Ser Phe Ala  
 1 5 10 15

Phe Phe Ser Gly His Arg Thr Leu Phe Phe Gly Val Arg Ser Pro  
 20 25 30

&lt;210&gt; 436

&lt;211&gt; 52

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 436

His Leu Ala Gln Thr Val Met Met His Pro Gln Lys Ser Phe Tyr Gln  
 1 5 10 15

Val Lys Asn Thr Asn His Ser Asp Arg Gly Ala Ile Glu Glu Thr Gln  
 20 25 30

Ile Leu Glu Asp Arg Leu Gly Gln Ile Pro Leu Cys Leu Glu Ser Gln  
 35 40 45

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Ile Trp Glu Ala  
50

<210> 437  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 437  
Lys Asn Thr Asn His Ser Asp Arg Gly Ala Ile Glu Glu Thr Gln Ile  
1 5 10 15

Leu Glu Asp Arg Leu Gly Gln Ile Pro Leu Cys Leu  
20 25

<210> 438  
<211> 73  
<212> PRT  
<213> Homo sapiens

<400> 438  
Gln Gly Cys Tyr Arg Arg Asp Ser Asn Ile Gly Arg Gln Val Arg Pro  
1 5 10 15

Asp Ser Ile Met Leu Arg Lys Pro Asp Leu Gly Ser Ile Thr His Tyr  
20 25 30

Gly Ser Val Leu Gly Asn Leu Asn Tyr Cys Asp Leu Pro Gln Leu Tyr  
35 40 45

Arg Asn Pro Ser Leu Gly Asn Ser Gly Met Arg Glu Met Phe Ser Pro  
50 55 60

Phe Tyr Asn Pro Val Glu Cys His Pro  
65 70

<210> 439  
<211> 23  
<212> PRT  
<213> Homo sapiens

<400> 439  
Pro Asp Ser Ile Met Leu Arg Lys Pro Asp Leu Gly Ser Ile Thr His  
1 5 10 15

Tyr Gly Ser Val Leu Gly Asn  
20

<210> 440  
<211> 22  
<212> PRT  
<213> Homo sapiens

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207

&lt;400&gt; 440

Tyr Arg Asn Pro Ser Leu Gly Asn Ser Gly Met Arg Glu Met Phe Ser  
 1 5 10 15

Pro Phe Tyr Asn Pro Val  
 20

&lt;210&gt; 441

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 441

Asn Ser Ala Arg Gly Leu Ser Gly Gly His Pro Phe Pro Trp Leu Ser  
 1 5 10 15

Glu Gly His Pro Phe  
 20

&lt;210&gt; 442

&lt;211&gt; 107

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 442

Thr Asp Ser Asp Leu Thr Leu Gly Ile Leu Leu Leu Gly Ile Tyr Thr  
 1 5 10 15

Asn His Ile Trp Glu Met Phe Leu Ala Ala Ser Arg Ile Asn Ser Pro  
 20 25 30

Lys Leu Glu Pro Glu Lys Ser Val Lys Arg Gln Ile Asn Phe Pro Ser  
 35 40 45

Ser Lys Asp Val Gly Cys Ser Leu Glu Val Pro Lys Asp Gly Pro Pro  
 50 55 60

Leu Ser His Gly Lys Glu Trp Ile Pro Leu Ser His Arg Lys Gly Trp  
 65 70 75 80

Ile Pro Leu Ser His Met Lys Gly Trp Pro Ser Leu Ser His Gly Lys  
 85 90 95

Gly Trp Pro Pro Leu Ser Pro Arg Ala Glu Phe  
 100 105

&lt;210&gt; 443

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 443

Leu Gly Ile Leu Leu Leu Gly Ile Tyr Thr Asn His Ile Trp Glu Met  
 1 5 10 15

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Phe Leu Ala Ala  
20

<210> 444  
<211> 27  
<212> PRT  
<213> Homo sapiens

<400> 444  
Lys Ser Val Lys Arg Gln Ile Asn Phe Pro Ser Ser Lys Asp Val Gly  
1 5 10 15

Cys Ser Leu Glu Val Pro Lys Asp Gly Pro Pro  
20 25

<210> 445  
<211> 27  
<212> PRT  
<213> Homo sapiens

<400> 445  
Gly Lys Glu Trp Ile Pro Leu Ser His Arg Lys Gly Trp Ile Pro Leu  
1 5 10 15

Ser His Met Lys Gly Trp Pro Ser Leu Ser His  
20 25

<210> 446  
<211> 47  
<212> PRT  
<213> Homo sapiens

<400> 446  
Gly Trp Ala Ser Thr Gln Pro Arg Glu Arg Met Asp Pro Ala Gln Pro  
1 5 10 15

Gln Glu Arg Met Asp Pro Ser Gln Pro His Glu Arg Met Ala Leu Thr  
20 25 30

Gln Pro Trp Lys Arg Met Ala Pro Thr Gln Pro Ser Cys Arg Ile  
35 40 45

<210> 447  
<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 447  
Pro Ala Gln Pro Gln Glu Arg Met Asp Pro Ser Gln Pro His Glu Arg  
1 5 10 15

Met Ala Leu Thr Gln Pro Trp Lys

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<210> 448  
 <211> 30  
 <212> PRT  
 <213> Homo sapiens

<400> 448  
 Ile Ala Asn Gly Gly Gly Arg Pro Ile Lys Leu Asn Ala Leu Tyr Lys  
           1                          5                          10                          15  
 Ile Gln Asn Glu Cys Lys Ile Val Phe Thr Cys Ile Asp Phe  
                           20                          25                          30

<210> 449  
 <211> 33  
 <212> PRT  
 <213> Homo sapiens

<400> 449  
 Met Pro Cys Ile Lys Ser Lys Met Asn Ala Lys Leu Phe Ser Leu Val  
           1                          5                          10                          15  
 Leu Thr Leu Cys Cys Met Ile Pro Ile Ser Val Leu Phe Gly Thr Cys  
                           20                          25                          30  
 Ile

<210> 450  
 <211> 101  
 <212> PRT  
 <213> Homo sapiens

<400> 450  
 Gln Val Ala Met Gly Ser Leu Ser Gly Leu Arg Leu Ala Ala Gly Ser  
           1                          5                          10                          15  
 Cys Phe Arg Leu Cys Glu Arg Asp Val Ser Ser Ser Leu Arg Leu Thr  
                           20                          25                          30  
 Arg Ser Ser Asp Leu Lys Arg Ile Asn Gly Phe Cys Thr Lys Pro Gln  
                           35                          40                          45  
 Glu Ser Pro Gly Ala Pro Ser Arg Thr Tyr Asn Arg Val Pro Leu His  
           50                          55                          60  
 Lys Pro Thr Asp Trp Gln Lys Lys Ile Leu Ile Trp Ser Gly Arg Phe  
           65                          70                          75                          80  
 Lys Lys Glu Asp Glu Ile Pro Glu Thr Val Ser Leu Glu Met Leu Asp  
                           85                          90                          95  
 Ala Ala Lys Asn Lys

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210

100

<210> 451  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<400> 451  
 Gly Leu Arg Leu Ala Ala Gly Ser Cys Phe Arg Leu Cys Glu Arg Asp  
           1                          5                          10                          15

Val Ser Ser Ser Leu Arg Leu Thr Arg  
                           20                          25

<210> 452  
 <211> 20  
 <212> PRT  
 <213> Homo sapiens

<400> 452  
 Ala Pro Ser Arg Thr Tyr Asn Arg Val Pro Leu His Lys Pro Thr Asp  
           1                          5                          10                          15

Trp Gln Lys Lys  
                           20

<210> 453  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 453  
 Ile Trp Ser Gly Arg Phe Lys Lys Glu Asp Glu Ile Pro Glu Thr Val  
           1                          5                          10                          15

Ser Leu Glu Met Leu Asp Ala  
                           20

<210> 454  
 <211> 63  
 <212> PRT  
 <213> Homo sapiens

<400> 454  
 Met Asp Phe Ala Gln Asn His Arg Lys Val Pro Glu Leu His Pro Ala  
           1                          5                          10                          15

Leu Thr Thr Glu Cys Leu Tyr Thr Asn Leu Arg Ile Gly Arg Lys Arg  
                           20                          25                          30

Ser Ser Tyr Gly Gln Val Ala Ser Lys Arg Lys Met Lys Ser Gln Arg  
           35                          40                          45

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211

Leu Ser Arg Trp Arg Cys Leu Met Leu Gln Arg Thr Arg Cys Glu  
 50 55 60

&lt;210&gt; 455

&lt;211&gt; 19

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 455

Lys Val Pro Glu Leu His Pro Ala Leu Thr Thr Glu Cys Leu Tyr Thr  
 1 5 10 15

Asn Leu Arg

&lt;210&gt; 456

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 456

Lys Arg Ser Ser Tyr Gly Gln Val Ala Ser Lys Arg Lys Met Lys Ser  
 1 5 10 15

Gln Arg Leu Ser Arg Trp Arg Cys Leu Met  
 20 25

&lt;210&gt; 457

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 457

Ile Asn Gly Phe Cys Thr Lys Pro Gln Glu Ser Pro  
 1 5 10

&lt;210&gt; 458

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 458

Arg Val Pro Leu His Lys Pro Thr Asp  
 1 5

&lt;210&gt; 459

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 459

Trp Ser Gly Arg Phe Lys Lys Glu

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1

5

<210> 460  
<211> 9  
<212> PRT  
<213> Homo sapiens

<400> 460  
Glu Met Leu Asp Ala Ala Lys Asn Lys  
1 5

<210> 461  
<211> 9  
<212> PRT  
<213> Homo sapiens

<400> 461  
Ser Tyr Leu Met Ile Ala Leu Thr Val  
1 5

<210> 462  
<211> 9  
<212> PRT  
<213> Homo sapiens

<400> 462  
Met Val Ile Glu Gly Lys Lys Ala Ala  
1 5

<210> 463  
<211> 68  
<212> PRT  
<213> Homo sapiens

<400> 463  
Arg Pro Gly Met Arg Ala Leu Gly Ser Cys Leu Ser Leu Leu Ala Leu  
1 5 10 15

Cys Ser Pro Gln Ala Arg Pro Gly Pro Arg Thr Leu Asp Ala Ser Thr  
20 25 30

Ala Thr Leu Thr Pro His Phe Ser Pro Cys Ala Arg Phe Ser Pro Val  
35 40 45

Gly Pro Ser Ala Val Pro Phe Ala Ala Thr Pro Leu Pro Leu Ala Gly  
50 55 60

Pro His Gln Pro  
65

<210> 464  
<211> 20

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213

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 464

Gly Ser Cys Leu Ser Leu Leu Ala Leu Cys Ser Pro Gln Ala Arg Pro  
1 5 10 15

Gly Pro Arg Thr  
20

&lt;210&gt; 465

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 465

His Phe Ser Pro Cys Ala Arg Phe Ser Pro Val Gly Pro Ser Ala Val  
1 5 10 15

Pro Phe Ala Ala Thr Pro Leu  
20

&lt;210&gt; 466

&lt;211&gt; 92

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (43)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (80)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 466

Ala Ile Glu Glu Arg Asn Lys Ser Arg Leu Thr Gln Gln Ala Ser Glu  
1 5 10 15

Pro Thr Gly Ser Pro Arg Tyr Leu His Glu Gln His Pro Gly Ser Arg  
20 25 30

Ser Gln Met Asp Cys Gly Ser Leu Thr Met Xaa Cys Pro Pro Pro Arg  
35 40 45

Val Arg Asp Asp Arg Thr Ser Ala Arg Gly Val Pro Arg Gln Ala Ala  
50 55 60

Pro Asp Ile Val Gly Gly Arg Pro Ser Ser Arg Ala Cys Val Ser Xaa  
65 70 75 80

Pro Ala Cys Ala Pro Ser Ala Ala Val Phe Pro Tyr  
85 90

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<210> 467  
 <211> 24  
 <212> PRT  
 <213> Homo sapiens

<400> 467  
 Leu Thr Gln Gln Ala Ser Glu Pro Thr Gly Ser Pro Arg Tyr Leu His  
           1                          5                          10                          15  
 Glu Gln His Pro Gly Ser Arg Ser  
                           20

<210> 468  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<400> 468  
 Ser Ala Arg Gly Val Pro Arg Gln Ala Ala Pro Asp Ile Val Gly Gly  
           1                          5                          10                          15  
 Arg Pro Ser Ser Arg Ala Cys Val Ser  
                           20                          25

<210> 469  
 <211> 14  
 <212> PRT  
 <213> Homo sapiens

<400> 469  
 Pro Arg Val Arg Lys Thr Pro His Leu Ser Ala Ser Gly Lys  
           1                          5                          10

<210> 470  
 <211> 59  
 <212> PRT  
 <213> Homo sapiens

<400> 470  
 Tyr Tyr Tyr Ser Met Leu Lys Ile Cys His Ile Thr Ile Leu Glu Thr  
           1                          5                          10                          15  
 Leu Ser Asp Arg Thr Pro Arg Lys Phe Ala Lys Lys Cys Tyr Ile Leu  
                           20                          25                          30  
 Tyr Ile Lys Leu Ser Asp Ser Ser Val Glu Lys Val Ala Tyr Thr Leu  
           35                          40                          45  
 Leu Leu Leu Ile Pro Ala Ala Ile Glu Lys Lys  
           50                          55

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215

<210> 471  
 <211> 32  
 <212> PRT  
 <213> Homo sapiens

<400> 471  
 Thr Ile Leu Glu Thr Leu Ser Asp Arg Thr Pro Arg Lys Phe Ala Lys  
           1                          5                          10                          15  
 Lys Cys Tyr Ile Leu Tyr Ile Lys Leu Ser Asp Ser Ser Val Glu Lys  
                           20                          25                          30

<210> 472  
 <211> 17  
 <212> PRT  
 <213> Homo sapiens

<400> 472  
 Val His Thr Lys Glu Ile Phe Arg Glu Arg Ser Ala Gly Phe Pro Val  
           1                          5                          10                          15  
 Lys

<210> 473  
 <211> 97  
 <212> PRT  
 <213> Homo sapiens

<400> 473  
 Leu Glu Met Gly Phe Gln Pro Thr Lys Glu Ile Asn Ala Arg Gly Ser  
           1                          5                          10                          15  
 Glu Pro Cys Gln Ala Gln Ser Thr Ser Leu Pro Lys Leu Pro Arg Trp  
                           20                          25                          30  
 Gly Ser Arg Pro Glu Ala Pro Gln Thr Pro Gln Gly Gly Leu Glu Ser  
                           35                          40                          45  
 Arg Cys Cys Thr Pro Val Ser Lys Gln Ser Leu Asn Leu Lys Ala Asp  
           50                          55                          60  
 Arg Phe Lys Ala Leu Thr Leu Gly Arg Ala Gln Trp Leu Thr Pro Val  
           65                          70                          75                          80  
 Ile Gln Ala Leu Ser Glu Leu Arg Trp Val Asp His Leu Arg Ser Gly  
                           85                          90                          95  
 Val

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216

<210> 474  
<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 474  
Phe Gln Pro Thr Lys Glu Ile Asn Ala Arg Gly Ser Glu Pro Cys Gln  
1 5 10 15  
Ala Gln Ser Thr Ser Leu Pro Lys  
20

<210> 475  
<211> 27  
<212> PRT  
<213> Homo sapiens

<400> 475  
Pro Lys Leu Pro Arg Trp Gly Ser Arg Pro Glu Ala Pro Gln Thr Pro  
1 5 10 15  
Gln Gly Gly Leu Glu Ser Arg Cys Cys Thr Pro  
20 25

<210> 476  
<211> 27  
<212> PRT  
<213> Homo sapiens

<400> 476  
Arg Phe Lys Ala Leu Thr Leu Gly Arg Ala Gln Trp Leu Thr Pro Val  
1 5 10 15  
Ile Gln Ala Leu Ser Glu Leu Arg Trp Val Asp  
20 25

<210> 477  
<211> 176  
<212> PRT  
<213> Homo sapiens

<400> 477  
Arg Ile Pro Leu Gln Ser Asp Gly Ser Phe Leu His Glu Lys Ser Ser  
1 5 10 15  
Gln Gln Arg Ser Asn Arg Asn Phe Pro Cys Pro Thr Leu Gln Cys Asn  
20 25 30  
Pro Glu Val Ser Phe Trp Phe Val Val Thr Asp Pro Ser Lys Asn His  
35 40 45  
Thr Leu Pro Ala Val Glu Val Gln Ser Ala Ile Arg Met Asn Lys Asn  
50 55 60

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217

Arg Ile Asn Asn Ala Phe Phe Leu Asn Asp Gln Thr Leu Glu Phe Leu  
 65 70 75 80

Lys Ile Pro Ser Thr Leu Ala Pro Pro Met Asp Pro Ser Val Pro Ile  
 85 90 95

Trp Ile Ile Ile Phe Gly Val Ile Phe Cys Ile Ile Ile Val Ala Ile  
 100 105 110

Ala Leu Leu Ile Leu Ser Gly Ile Trp Gln Arg Arg Arg Lys Asn Lys  
 115 120 125

Glu Pro Ser Glu Val Asp Asp Ala Glu Asp Lys Cys Glu Asn Met Ile  
 130 135 140

Thr Ile Glu Asn Gly Ile Pro Ser Asp Pro Leu Asp Met Lys Gly Gly  
 145 150 155 160

His Ile Asn Asp Ala Phe Met Thr Glu Asp Glu Arg Leu Thr Pro Leu  
 165 170 175

&lt;210&gt; 478

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 478

Pro Cys Pro Thr Leu Gln Cys Asn Pro Glu Val Ser Phe Trp Phe Val  
 1 5 10 15

Val Thr Asp Pro Ser Lys Asn His Thr  
 20 25

&lt;210&gt; 479

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 479

Ala Ile Arg Met Asn Lys Asn Arg Ile Asn Asn Ala Phe Phe Leu Asn  
 1 5 10 15

Asp Gln Thr Leu Glu Phe Leu  
 20

&lt;210&gt; 480

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 480

SUBSTITUTE SHEET (RULE 26)

218

Ile Trp Gln Arg Arg Arg Lys Asn Lys Glu Pro Ser Glu Val Asp Asp  
 1 5 10 15

Ala Glu Asp Lys Cys Glu Asn Met  
 20

&lt;210&gt; 481

&lt;211&gt; 19

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 481

Pro Leu Asp Met Lys Gly Gly His Ile Asn Asp Ala Phe Met Thr Glu  
 1 5 10 15

Asp Glu Arg

&lt;210&gt; 482

&lt;211&gt; 136

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 482

Gly Ser Arg Thr Thr Ala Leu Gln Arg Gly Val Ser Leu Ser Ser Ser  
 1 5 10 15

Val Met Lys Ala Ser Leu Ile Cys Pro Pro Phe Met Ser Arg Gly Ser  
 20 25 30

Glu Gly Met Pro Phe Ser Ile Val Ile Met Phe Ser His Leu Ser Ser  
 35 40 45

Ala Ser Ser Thr Ser Asp Gly Ser Leu Phe Phe Leu Leu Arg Cys Gln  
 50 55 60

Ile Pro Asp Lys Ile Ser Ser Ala Ile Ala Thr Met Met Met Gln Asn  
 65 70 75 80

Ile Thr Pro Asn Ile Ile Ile Gln Met Gly Thr Asp Gly Ser Met Gly  
 85 90 95

Gly Ala Ser Val Glu Gly Ile Phe Lys Asn Ser Arg Val Trp Ser Phe  
 100 105 110

Arg Lys Lys Ala Leu Leu Ile Arg Phe Leu Phe Ile Leu Met Ala Asp  
 115 120 125

Cys Thr Ser Thr Ala Gly Arg Val  
 130 135

&lt;210&gt; 483

&lt;211&gt; 28

&lt;212&gt; PRT

SUBSTITUTE SHEET (RULE 26)

219

&lt;213&gt; Homo sapiens

&lt;400&gt; 483

Val Ser Leu Ser Ser Ser Val Met Lys Ala Ser Leu Ile Cys Pro Pro  
 1 5 10 15

Phe Met Ser Arg Gly Ser Glu Gly Met Pro Phe Ser  
 20 25

&lt;210&gt; 484

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 484

Ser Met Gly Gly Ala Ser Val Glu Gly Ile Phe Lys Asn Ser Arg Val  
 1 5 10 15

Trp Ser Phe Arg Lys Lys Ala Leu  
 20

&lt;210&gt; 485

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 485

Gly Ala Arg Gly Ser Gln Gln Asp Ala Pro Ala Leu Gln Glu Ala Glu  
 1 5 10 15

Val Arg Gly Pro Glu Arg Ala Gln Pro Ala Arg Gly Arg  
 20 25

&lt;210&gt; 486

&lt;211&gt; 439

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 486

Ser Glu Arg Pro Gly Glu Gly Pro Ala Arg Pro Gly Gln Asp Asp Gln  
 1 5 10 15

Gly Pro Ala Val Pro Ala Val Ala Gly Ala Gly Val Gly Val His Asp  
 20 25 30

Pro Ala Asp His Arg Val Leu Gly Gln Arg Ser Ala Ala His Phe Tyr  
 35 40 45

Leu His Thr Ser Phe Ser Arg Pro His Thr Gly Pro Pro Leu Pro Thr  
 50 55 60

Pro Gly Pro Asp Arg Thr Gly Ser Ser Arg Pro Thr Pro Met Ser Thr  
 65 70 75 80

SUBSTITUTE SHEET (RULE 26)

220

Ser	Phe	Trp	Thr	Ile	Ser	His	Ala	Gly	Val	Lys	Gln	Ser	Asp	Leu	Pro	85	90	95
Arg	Lys	Glu	Thr	Glu	Gln	Pro	Pro	Ala	Pro	Gly	Glu	His	Gly	Gly	Glu	100	105	110
Arg	Glu	Arg	Leu	Arg	Leu	Val	Pro	Ala	Arg	Arg	Pro	Ala	Gln	Pro	Arg	115	120	125
Pro	Gly	Pro	Ala	Ala	Gly	Gly	Ala	Glu	Glu	Arg	Ala	Ala	Gly	Leu	Leu	130	135	140
Arg	Gln	Leu	Gln	Pro	Gly	Leu	Pro	His	Gln	Gly	Ala	Arg	Ile	Arg	Arg	145	150	155
His	Pro	Gln	Leu	Gly	Ala	Glu	Pro	Pro	Asp	Arg	Gly	Arg	Pro	Ala	Arg	165	170	175
Gly	His	Leu	Leu	Leu	Arg	Ala	Gln	Gly	Gly	Leu	His	Gln	Leu	Glu	Ala	180	185	190
Arg	Asp	Asp	Arg	Ala	Glu	Arg	Lys	Pro	Ala	Ala	Pro	Arg	Cys	Ala	Leu	195	200	205
Pro	Arg	Pro	Ala	Ala	His	Pro	Ala	Arg	Ala	Arg	Ala	Gln	Arg	Gln	Arg	210	215	220
Ala	Pro	Asp	Leu	Gln	Gln	Val	Leu	Ala	Pro	Leu	Arg	Glu	Ala	Leu	Pro	225	230	235
Pro	Pro	His	Glu	Gly	Gln	Ala	Gln	Glu	Val	His	Gln	Val	Pro	Leu	Arg	245	250	255
Ala	Arg	Pro	Leu	Arg	Ala	Pro	Asp	Leu	Arg	Leu	Pro	Gln	Gln	Val	Arg	260	265	270
Ala	Gly	Glu	Arg	Gly	Val	Leu	Pro	Gln	Val	Arg	Arg	Ala	His	Ala	Ala	275	280	285
Gly	Val	Arg	Gln	Pro	His	Gln	Pro	Ala	Arg	Leu	Gly	Ala	Arg	Gly	Leu	290	295	300
Pro	Arg	Trp	Pro	Gln	Gly	Val	Leu	Arg	Gln	Leu	His	Pro	Val	Pro	Ala	305	310	315
Gly	Pro	Ala	His	Gly	Glu	Ala	Gly	Ala	Leu	Gln	Arg	Ala	Leu	Ala	Ala	325	330	335
Gly	Val	Pro	Pro	Leu	Pro	Pro	Val	Pro	Asp	Arg	Leu	Arg	Phe	Leu	Gly	340	345	350
Lys	Leu	Glu	Thr	Leu	Asp	Glu	Asp	Ala	Ala	Gln	Leu	Leu	Gln	Leu	Leu	355	360	365
Gln	Val	Asp	Arg	Gln	Ser	Ala	Ser	Pro	Arg	Ala	Thr	Gly	Thr	Gly	Pro	370	375	380

SUBSTITUTE SHEET (RULE 26)

221

Pro Ala Ala Gly Arg Arg Thr Gly Ser Pro Arg Ser Pro Trp Pro Gly  
 385 390 395 400

Gly Ser Ser Cys Ile Asn Ser Thr Arg Pro Thr Leu Phe Ser Ser Ala  
 405 410 415

Thr Pro Ser Pro Lys Thr Ser Ser Glu Thr Glu Ser Phe Arg Val Ala  
 420 425 430

Phe Ser Arg Val Pro Gly Thr  
 435

&lt;210&gt; 487

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 487

Arg Pro Gly Gln Asp Asp Gln Gly Pro Ala Val Pro Ala Val Ala Gly  
 1 5 10 15

Ala Gly Val Gly Val His Asp Pro Ala  
 20 25

&lt;210&gt; 488

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 488

Ser Arg Pro His Thr Gly Pro Pro Leu Pro Thr Pro Gly Pro Asp Arg  
 1 5 10 15

Thr Gly Ser Ser Arg  
 20

&lt;210&gt; 489

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 489

Ser His Ala Gly Val Lys Gln Ser Asp Leu Pro Arg Lys Glu Thr Glu  
 1 5 10 15

Gln Pro Pro Ala Pro Gly Glu  
 20

&lt;210&gt; 490

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

SUBSTITUTE SHEET (RULE 26)

222

&lt;400&gt; 490

Arg Arg Pro Ala Gln Pro Arg Pro Gly Pro Ala Ala Gly Gly Ala Glu  
1 5 10 15

Glu Arg Ala Ala Gly Leu Leu  
20

&lt;210&gt; 491

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 491

Arg Arg His Pro Gln Leu Gly Ala Glu Pro Pro Asp Arg Gly Arg Pro  
1 5 10 15

Ala Arg Gly His Leu Leu Leu  
20

&lt;210&gt; 492

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 492

Arg Asp Asp Arg Ala Glu Arg Lys Pro Ala Ala Pro Arg Cys Ala Leu  
1 5 10 15

Pro Arg Pro Ala Ala His Pro Ala Arg  
20 25

&lt;210&gt; 493

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 493

Arg Ala Pro Asp Leu Gln Gln Val Leu Ala Pro Leu Arg Glu Ala Leu  
1 5 10 15

Pro Pro Pro His Glu Gly Gln Ala Gln Glu Val  
20 25

&lt;210&gt; 494

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 494

Asp Leu Arg Leu Pro Gln Gln Val Arg Ala Gly Glu Arg Gly Val Leu  
1 5 10 15

Pro Gln Val Arg Arg Ala His Ala Ala Gly

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223

20

25

&lt;210&gt; 495

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 495

Gln Pro Ala Arg Leu Gly Ala Arg Gly Leu Pro Arg Trp Pro Gln Gly  
 1 5 10 15

Val Leu Arg Gln Leu His Pro Val Pro Ala Gly  
 20 25

&lt;210&gt; 496

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 496

Ala Gly Val Pro Pro Leu Pro Pro Val Pro Asp Arg Leu Arg Phe Leu  
 1 5 10 15

Gly Lys Leu Glu Thr Leu Asp Glu  
 20

&lt;210&gt; 497

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 497

Gln Leu Leu Gln Leu Leu Gln Val Asp Arg Gln Ser Ala Ser Pro Arg  
 1 5 10 15

Ala Thr Gly Thr Gly Pro Pro Ala Ala  
 20 25

&lt;210&gt; 498

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 498

Asn Ser Thr Arg Pro Thr Leu Phe Ser Ser Ala Thr Pro Ser Pro Lys  
 1 5 10 15

Thr Ser Ser Glu Thr Glu Ser Phe Arg  
 20 25

&lt;210&gt; 499

&lt;211&gt; 324

SUBSTITUTE SHEET (RULE 26)

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 499

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Leu Gly Gly Lys Arg Thr Ala Gly Pro Pro Gly Val Ala Ala Ala Ala
 1           5           10           15

Ala Arg Arg Pro Arg Pro Glu Ser Pro Ala Ser Pro Gly Ile Val Val
          20           25           30

Asp Leu Ala Arg Val Ala Glu Ala Val His Leu Pro Pro Val Leu Val
          35           40           45

Glu Gly Arg Gln Leu Leu Arg Val Arg Val Gln Gln Val Leu Asp Glu
          50           55           60

Val Gly Glu Gly His Leu Glu Ala Ser Ala Glu Gly Leu Ala Arg Arg
          65           70           75           80

Gly Gly Gln Ala Gly Val Val Gly Val His Pro Gln His Gly His Gly
          85           90           95

Glu Leu Ala Val Glu Leu Leu Val Leu Gln Leu Glu Leu Ala Ala Glu
          100          105          110

Gly Gly Asp Gln Ala His Glu Gly Val Ala His Glu Glu Glu Leu Gly
          115          120          125

Val Leu Leu Glu Leu Asp Leu His Glu Val Ala Gly Glu Leu Pro Val
          130          135          140

Ala Ala Pro Glu Leu Val Glu Gly Gln Val Arg Ala Gly Val Val His
          145          150          155          160

Val Leu Ala Arg Asp Ala Gln Arg Val Ala Val Gly Arg Thr Ala Val
          165          170          175

Gln Gln Ala Ser Ala Gln His Asp His His Ala Leu Pro Val Gly Ala
          180          185          190

Gly His Leu Gly His Val Ala Val Asp Gly Pro Val Pro Val Val His
          195          200          205

Asp Gln Val Ala Gln Leu Arg Val Gly Asp Val Val Glu Cys Ala Leu
          210          215          220

Leu Gly Gly Glu Gly Gln Ala Gly Val Gly Ala Glu Ala Pro Gln His
          225          230          235          240

Val Pro Pro Leu Arg Leu Leu Pro Ala Leu Val Trp Ala Ala Pro Gly
          245          250          255

Val Ala Arg Gly Pro Val Val Ala Ser His Ala Leu Leu His Ala Pro
          260          265          270

Pro Ala Gln Ala Ala Ala Pro Ser Pro Phe Trp Glu Gly His Ser Ala
          275          280          285

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SUBSTITUTE SHEET (RULE 26)

225

Ser Arg Gln His Glu Lys Leu Ser Arg Asn Ser Ser Thr Ser Glu Ser  
 290 295 300

Ala Val Ser Ser Leu Ser Cys Pro Ala Arg Ala Trp Ala Ala Ala Ala  
 305 310 315 320

Pro Cys Ala Ala

<210> 500

<211> 23

<212> PRT

<213> Homo sapiens

<400> 500

Glu Ala Val His Leu Pro Pro Val Leu Val Glu Gly Arg Gln Leu Leu  
 1 5 10 15

Arg Val Arg Val Gln Gln Val  
 20

<210> 501

<211> 24

<212> PRT

<213> Homo sapiens

<400> 501

Gly His Leu Glu Ala Ser Ala Glu Gly Leu Ala Arg Arg Gly Gly Gln  
 1 5 10 15

Ala Gly Val Val Gly Val His Pro  
 20

<210> 502

<211> 28

<212> PRT

<213> Homo sapiens

<400> 502

Gln Leu Glu Leu Ala Ala Glu Gly Gly Asp Gln Ala His Glu Gly Val  
 1 5 10 15

Ala His Glu Glu Glu Leu Gly Val Leu Leu Glu Leu  
 20 25

<210> 503

<211> 27

<212> PRT

<213> Homo sapiens

<400> 503

Gly Glu Leu Pro Val Ala Ala Pro Glu Leu Val Glu Gly Gln Val Arg

**SUBSTITUTE SHEET (RULE 26)**

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&lt;210&gt; 508

&lt;211&gt; 314

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 508

Ser Arg Val Thr Phe Pro Glu Arg Arg Arg Ser Ser Arg Leu Arg Arg

1

5

10

15

Gly Ser Met Glu Glu Ser Val Arg Gly Tyr Asp Trp Ser Pro Arg Asp

20

25

30

Ala Arg Arg Ser Pro Asp Gln Gly Arg Gln Gln Ala Glu Arg Arg Asn

35

40

45

Val Leu Arg Gly Phe Cys Ala Asn Ser Ser Leu Ala Phe Pro Thr Lys

50

55

60

Glu Arg Ala Phe Asp Asp Ile Pro Asn Ser Glu Leu Ser His Leu Ile

65

70

75

80

Val Asp Asp Arg His Gly Ala Ile Tyr Cys Tyr Val Pro Lys Val Ala

85

90

95

Cys Thr Asn Trp Lys Arg Val Met Ile Val Leu Ser Gly Ser Leu Leu

100

105

110

His Arg Gly Ala Pro Tyr Arg Asp Pro Leu Arg Ile Pro Arg Glu His

115

120

125

Val His Asn Ala Ser Ala His Leu Thr Phe Asn Lys Phe Trp Arg Arg

130

135

140

Tyr Gly Lys Leu Ser Arg His Leu Met Lys Val Lys Leu Lys Lys Tyr

145

150

155

160

Thr Lys Phe Leu Phe Val Arg Asp Pro Phe Val Arg Leu Ile Ser Ala

165

170

175

Phe Arg Ser Lys Phe Glu Leu Glu Asn Glu Glu Phe Tyr Arg Lys Phe

180

185

190

Ala Val Pro Met Leu Arg Val Tyr Ala Asn His Thr Ser Leu Pro Ala

195

200

205

Ser Ala Arg Glu Ala Phe Arg Ala Gly Leu Lys Val Ser Phe Ala Asn

210

215

220

Phe Ile Gln Tyr Leu Leu Asp Pro His Thr Glu Lys Leu Ala Pro Phe

225

230

235

240

Asn Glu His Trp Arg Gln Val Tyr Arg Leu Cys His Pro Cys Gln Ile

245

250

255

Asp Tyr Asp Ser Trp Gly Ser Trp Arg Leu Trp Thr Arg Thr Pro Arg

260

265

270

SUBSTITUTE SHEET (RULE 26)

228

Ser Cys Cys Ser Tyr Ser Arg Trp Thr Gly Ser Pro Leu Pro Pro Glu  
 275 280 285

Leu Pro Glu Gln Asp Arg Gln Gln Leu Gly Gly Gly Leu Val Arg Gln  
 290 295 300

Asp Pro Pro Gly Leu Glu Ala Ala Ala Val  
 305 310

<210> 509  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 509  
 Arg Ser Pro Asp Gln Gly Arg Gln Gln Ala Glu Arg Arg Asn Val Leu  
 1 5 10 15

Arg Gly Phe Cys Ala Asn Ser Ser Leu Ala  
 20 25

<210> 510  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 510  
 Thr Lys Glu Arg Ala Phe Asp Asp Ile Pro Asn Ser Glu Leu Ser His  
 1 5 10 15

Leu Ile Val Asp Asp Arg His Gly Ala Ile Tyr Cys  
 20 25

<210> 511  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 511  
 Phe Asn Lys Phe Trp Arg Arg Tyr Gly Lys Leu Ser Arg His Leu Met  
 1 5 10 15

Lys Val Lys Leu Lys Lys Tyr  
 20

<210> 512  
 <211> 24  
 <212> PRT  
 <213> Homo sapiens

<400> 512  
 Phe Val Arg Leu Ile Ser Ala Phe Arg Ser Lys Phe Glu Leu Glu Asn

SUBSTITUTE SHEET (RULE 26)

229

1                      5                      10                      15

Glu Glu Phe Tyr Arg Lys Phe Ala  
20

&lt;210&gt; 513

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 513

Thr Ser Leu Pro Ala Ser Ala Arg Glu Ala Phe Arg Ala Gly Leu Lys  
1                      5                      10                      15

Val Ser Phe Ala Asn Phe Ile Gln Tyr Leu  
20                      25

&lt;210&gt; 514

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 514

Ser Tyr Ser Arg Trp Thr Gly Ser Pro Leu Pro Pro Glu Leu Pro Glu  
1                      5                      10                      15

Gln Asp Arg Gln Gln Leu Gly Gly Gly  
20                      25

&lt;210&gt; 515

&lt;211&gt; 6

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 515

Ser Thr Gly Cys Ser Glu  
1                      5

&lt;210&gt; 516

&lt;211&gt; 146

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 516

Cys Leu Cys Leu Gly Cys Gly Leu Pro Glu Leu His Ser Tyr Leu Asp  
1                      5                      10                      15

Pro Gly Pro Tyr Leu Leu Val Tyr Pro Thr Leu Phe Trp Leu Cys Pro  
20                      25                      30

Ser Ala Val Ser Pro Trp Ala Tyr Thr Cys Tyr Gln Leu Gly Leu Gly  
35                      40                      45

SUBSTITUTE SHEET (RULE 26)

230

Pro Gln Trp Gly Ala Ala Ala Leu Ser Phe Thr Val Asp Ala Ala Ile  
 50 55 60

Arg Val Trp Asp Val Ser Thr Glu Thr Cys Val Pro Leu Pro Trp Phe  
 65 70 75 80

Arg Gly Gly Gly Val Thr Asn Cys Ser Gly Pro Gln Thr Ala Ala Lys  
 85 90 95

Ser Trp Leu Pro Leu Leu Gln Leu Ser Phe Glu Ser Gly Arg Pro Arg  
 100 105 110

Cys Gly Leu Val Arg Gly Gly Leu Leu Tyr Gln Gly Ala Val Arg Leu  
 115 120 125

Ala Ala Gly Ala Gln Met Ala Ala Asp Cys Cys Ser Leu Tyr Trp Glu  
 130 135 140

Ser His  
 145

&lt;210&gt; 517

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 517

Tyr Pro Thr Leu Phe Trp Leu Cys Pro Ser Ala Val Ser Pro Trp Ala  
 1 5 10 15

Tyr Thr Cys Tyr Gln Leu Gly Leu Gly Pro  
 20 25

&lt;210&gt; 518

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 518

Asp Val Ser Thr Glu Thr Cys Val Pro Leu Pro Trp Phe Arg Gly Gly  
 1 5 10 15

Gly Val Thr Asn Cys Ser Gly Pro Gln  
 20 25

&lt;210&gt; 519

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 519

Leu Leu Tyr Gln Gly Ala Val Arg Leu Ala Ala Gly Ala Gln Met Ala  
 1 5 10 15

SUBSTITUTE SHEET (RULE 26)



231

Ala Asp Cys Cys Ser Leu  
20

<210> 520  
<211> 155  
<212> PRT  
<213> Homo sapiens

<400> 520  
Asn Lys Arg Lys Thr Tyr Leu Phe Leu Glu Val Gly Met Trp Gly Val  
1 5 10 15  
Gly Gln Asn Arg Trp Trp Pro Trp Glu Arg Val Pro Arg Gly Arg Gly  
20 25 30  
Trp Gly Cys Leu Ser Lys Glu Gly Gln Val Met Asn Arg Ala Ser Thr  
35 40 45  
Pro Ser Arg Gly Phe Leu Gly Pro Pro Lys His Trp Ala Lys Thr Trp  
50 55 60  
Lys Leu Gly Ile Asp Lys Val Gln Arg Asp Val Gly Asn Ser Ala Cys  
65 70 75 80  
Gly Pro Ala His Thr Glu Gln Gly Pro Phe Val Glu Gly Arg Trp Lys  
85 90 95  
Val Met Ser Trp Gly Trp Ala Pro Gly Ser Pro Trp Ile Met Pro Gln  
100 105 110  
Gly Arg Ser Ser Asn Thr Gly Leu Phe Arg Val Arg Lys Arg Arg Met  
115 120 125  
Thr Gly Leu Pro Ser Cys Thr Leu Gly Phe Pro Phe Ile Ser Thr Ala  
130 135 140  
Arg Arg Ser Pro Leu Gly Ser Gln Thr Met Glu  
145 150 155

<210> 521  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 521  
Gly Val Gly Gln Asn Arg Trp Trp Pro Trp Glu Arg Val Pro Arg Gly  
1 5 10 15  
Arg Gly Trp Gly Cys Leu Ser Lys Glu Gly  
20 25

<210> 522  
<211> 26  
<212> PRT

SUBSTITUTE SHEET (RULE 26)

232

&lt;213&gt; Homo sapiens

&lt;400&gt; 522

Ala Lys Thr Trp Lys Leu Gly Ile Asp Lys Val Gln Arg Asp Val Gly  
1 5 10 15

Asn Ser Ala Cys Gly Pro Ala His Thr Glu  
20 25

&lt;210&gt; 523

&lt;211&gt; 42

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 523

Trp Ala Pro Gly Ser Pro Trp Ile Met Pro Gln Gly Arg Ser Ser Asn  
1 5 10 15

Thr Gly Leu Phe Arg Val Arg Lys Arg Arg Met Thr Gly Leu Pro Ser  
20 25 30

Cys Thr Leu Gly Phe Pro Phe Ile Ser Thr  
35 40

&lt;210&gt; 524

&lt;211&gt; 17

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 524

Ser Ser Tyr Gln Cys Pro Lys Val Thr Phe Phe Lys Ser Ser Val Asp  
1 5 10 15

Thr

&lt;210&gt; 525

&lt;211&gt; 14

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 525

Tyr Ile Tyr Ser Tyr Leu Gly Phe Phe Asn Gln Ile Asn Lys  
1 5 10

&lt;210&gt; 526

&lt;211&gt; 6

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 526

Ala Arg Asp Leu Ile Leu  
1 5

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&lt;210&gt; 527

&lt;211&gt; 43

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 527

Leu Thr Phe Tyr Leu Gln Phe Leu Ala Pro Lys Asp Lys Pro Ser Gly  
 1 5 10 15

Asp Thr Ala Ala Val Phe Glu Glu Gly Gly Asp Val Asp Asp Leu Val  
 20 25 30

Ser Thr Phe Asn Met His Leu Val Phe Cys Asp  
 35 40

&lt;210&gt; 528

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 528

Phe Leu Ala Pro Lys Asp Lys Pro Ser Gly Asp Thr Ala Ala Val Phe  
 1 5 10 15

Glu Glu Gly Gly Asp Val Asp Asp Leu  
 20 25

&lt;210&gt; 529

&lt;211&gt; 13

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 529

Ala Arg Ala Gly Ala Lys Ile Leu Phe Glu Gly Glu Phe  
 1 5 10

&lt;210&gt; 530

&lt;211&gt; 92

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 530

Asn Phe Glu Ile His Ser Ala Phe Pro Phe Met Leu Phe Val Ala Cys  
 1 5 10 15

Leu Leu His Ser Ser Cys Pro Arg Thr Ala Arg Phe Leu Ala Ser Pro  
 20 25 30

Leu Ser Glu Ser Asn Val Ile Phe Tyr Gln Asn Gln Tyr Gln Phe Pro  
 35 40 45

Cys Ile Leu Cys Phe Ile Glu Phe Ala Arg Leu Thr Ser Phe Lys His

SUBSTITUTE SHEET (RULE 26)

234

50                                      55                                      60  
 Leu Ile His Ser Gln Ser His Leu Val Arg Leu Gln Tyr Glu Asp Phe  
 65                                      70                                      75                                      80  
 Ser Val Ser Ser Glu Ala Trp Asp Thr Glu Leu Thr  
                                     85                                      90

<210> 531  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 531  
 Phe Pro Phe Met Leu Phe Val Ala Cys Leu Leu His Ser Ser Cys Pro  
 1                                      5                                      10                                      15  
 Arg Thr Ala Arg Phe Leu Ala Ser Pro Leu  
                                     20                                      25

<210> 532  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 532  
 Asn Val Ile Phe Tyr Gln Asn Gln Tyr Gln Phe Pro Cys Ile Leu Cys  
 1                                      5                                      10                                      15  
 Phe Ile Glu Phe Ala Arg Leu Thr Ser Phe  
                                     20                                      25

<210> 533  
 <211> 23  
 <212> PRT  
 <213> Homo sapiens

<400> 533  
 Ser Gln Ser His Leu Val Arg Leu Gln Tyr Glu Asp Phe Ser Val Ser  
 1                                      5                                      10                                      15  
 Ser Glu Ala Trp Asp Thr Glu  
                                     20

<210> 534  
 <211> 10  
 <212> PRT  
 <213> Homo sapiens

<400> 534  
 Gln Lys Phe Leu Cys Ala Ser Asp Gly Asp  
 1                                      5                                      10

SUBSTITUTE SHEET (RULE 26)

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<220>  
<221> SITE  
<222> (160)  
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (162)
<223> Xaa equals any of the naturally occurring L-amino acids
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<400> 535																
Ala	Glu	Val	Pro	Leu	Arg	Val	Arg	Arg	Arg	His	Gly	Arg	Pro	His	Gly	
1				5					10					15		
Pro	Gly	Gly	Arg	Gln	Leu	Ala	Leu	Gly	Ile	Pro	Ala	Leu	Arg	Ser	Leu	
			20					25					30			
Pro	Gly	Cys	Val	Pro	Arg	His	His	Gly	Cys	Ser	Pro	Gly	Tyr	Gly	Cys	
		35					40					45				
Leu	His	Arg	Arg	Ile	Leu	Cys	Leu	Pro	Leu	Ile	Leu	Leu	Leu	Val	Tyr	
	50					55					60					
Lys	Gln	Arg	Gln	Ala	Ala	Ser	Asn	Arg	Arg	Ala	Gln	Glu	Leu	Val	Arg	
65					70					75					80	
Met	Asp	Ser	Asn	Ile	Gln	Gly	Ile	Glu	Asn	Pro	Gly	Phe	Glu	Ala	Ser	
				85					90					95		
Pro	Pro	Ala	Gln	Gly	Ile	Pro	Glu	Ala	Lys	Val	Arg	His	Pro	Leu	Ser	
			100					105					110			
Tyr	Val	Ala	Gln	Arg	Gln	Pro	Ser	Glu	Ser	Gly	Arg	His	Leu	Leu	Ser	
		115					120					125				
Glu	Pro	Ser	Thr	Pro	Leu	Ser	Pro	Pro	Gly	Pro	Gly	Asp	Val	Phe	Phe	
	130					135					140					
Pro	Ser	Leu	Asp	Pro	Val	Pro	Asp	Ser	Pro	Asn	Phe	Glu	Val	Ile	Xaa	
145					150					155					160	
Pro	Xaa	Trp	Gly	Thr	Val	Gly	Cys	Cys	Gly	Trp	Val	Trp	Gly	Arg	Cys	
				165					170					175		

Ile

```
<210> 536
<211> 27
<212> PRT
```

236

&lt;213&gt; Homo sapiens

&lt;400&gt; 536

Gly Pro Gly Gly Arg Gln Leu Ala Leu Gly Ile Pro Ala Leu Arg Ser  
 1 5 10 15

Leu Pro Gly Cys Val Pro Arg His His Gly Cys  
 20 25

&lt;210&gt; 537

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 537

Phe Glu Ala Ser Pro Pro Ala Gln Gly Ile Pro Glu Ala Lys Val Arg  
 1 5 10 15

His Pro Leu Ser Tyr Val Ala Gln Arg  
 20 25

&lt;210&gt; 538

&lt;211&gt; 88

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 538

Asp Met Ser Leu Gly Met Trp Gln His Gln Trp Asp Lys Met Asp Thr  
 1 5 10 15

Gly Pro Pro Ser Gln Ala Pro Asp Thr Gly His Gly Gly Glu Thr Ser  
 20 25 30

Pro Pro Trp His Ala Leu Gly Ser Pro Val Leu Pro Glu Ala Ala Leu  
 35 40 45

Leu Ser Asp Phe Leu Phe Val Pro Gln Trp Leu Trp Gly Gln Ala Cys  
 50 55 60

Leu Pro Thr Gly His Arg His Leu Pro Gln Leu Pro Pro Thr Ser Ser  
 65 70 75 80

Phe Ser Glu Asp Leu Ser Thr Gly  
 85

&lt;210&gt; 539

&lt;211&gt; 78

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 539

Pro Val Asp Arg Ser Ser Glu Lys Leu Leu Val Gly Gly Ser Trp Gly  
 1 5 10 15

SUBSTITUTE SHEET (RULE 26)

237

Arg Trp Arg Trp Pro Val Gly Arg Gln Ala Trp Pro Gln Ser His Cys  
                     20                    25                    30

Gly Thr Lys Arg Lys Ser Asp Arg Arg Ala Ala Ser Gly Lys Thr Gly  
           35                    40                    45

Glu Pro Ser Ala Cys His Gly Gly Glu Val Ser Pro Pro Cys Pro Val  
       50                    55                    60

Ser Gly Ala Trp Glu Gly Gly Pro Val Ser Ile Leu Ser His  
   65                    70                    75

&lt;210&gt; 540

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 540

Pro Val Asp Arg Ser Ser Glu Lys Leu Leu Val Gly Gly Ser Trp Gly  
   1                    5                    10                    15

Arg Trp Arg Trp Pro Val  
                     20

&lt;210&gt; 541

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 541

Thr Lys Arg Lys Ser Asp Arg Arg Ala Ala Ser Gly Lys Thr Gly Glu  
   1                    5                    10                    15

Pro Ser Ala Cys His Gly Gly Glu Val  
                     20                    25

&lt;210&gt; 542

&lt;211&gt; 46

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 542

Met Thr Ser Lys Phe Gly Glu Ser Gly Thr Gly Ser Arg Asp Gly Lys  
   1                    5                    10                    15

Lys Thr Ser Pro Gly Pro Gly Gly Asp Arg Gly Val Leu Gly Ser Glu  
           20                    25                    30

Ser Arg Cys Arg Pro Asp Ser Glu Gly Cys Arg Trp Ala Thr  
       35                    40                    45

&lt;210&gt; 543

&lt;211&gt; 20

SUBSTITUTE SHEET (RULE 26)

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 543

Ser Pro Gly Pro Gly Gly Asp Arg Gly Val Leu Gly Ser Glu Ser Arg  
1 5 10 15

Cys Arg Pro Asp  
20

&lt;210&gt; 544

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 544

Pro Pro Ser Gln Ala Pro Asp Thr Gly His Gly Gly Glu Thr Ser Pro  
1 5 10 15

Pro Trp His Ala Leu Gly Ser  
20

&lt;210&gt; 545

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 545

His Glu Val Gln Pro Ser Tyr Leu Pro Ser Asn Ser Gly Leu Ile  
1 5 10 15

&lt;210&gt; 546

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 546

Leu Arg Ile Ser Val Leu Cys Arg Glu Thr Ala Cys Asn Trp Ser His  
1 5 10 15

His Pro Leu Asp Ser Asn  
20

&lt;210&gt; 547

&lt;211&gt; 32

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 547

Leu Thr Val Thr Val Arg Asn Pro Gly Ser Thr His Ala Ser Gly Arg  
1 5 10 15

Pro Arg Arg Arg Ser Gly Val Trp Ala Arg Arg Gly Leu Val Trp Gln

SUBSTITUTE SHEET (RULE 26)



239

20

25

30

<210> 548  
 <211> 38  
 <212> PRT  
 <213> Homo sapiens

<400> 548  
 Thr Pro Cys Ser Ala Gln Phe Ser Val Leu Gly Pro Ser Gly Pro Ile  
 1 5 10 15  
 Leu Ala Met Val Gly Glu Asp Ala Asp Leu Pro Cys His Leu Phe Pro  
 20 25 30  
 Thr Met Ser Ala Glu Thr  
 35

<210> 549  
 <211> 60  
 <212> PRT  
 <213> Homo sapiens

<400> 549  
 Met Glu Leu Lys Trp Val Ser Ser Ser Leu Arg Gln Val Val Asn Val  
 1 5 10 15  
 Tyr Ala Asp Gly Lys Glu Val Glu Asp Arg Gln Ser Ala Pro Tyr Arg  
 20 25 30  
 Gly Arg Thr Ser Ile Leu Arg Asp Gly Ile Thr Ala Gly Lys Ala Ala  
 35 40 45  
 Leu Arg Ile His Asn Val Thr Ala Ser Asp Ser Gly  
 50 55 60

<210> 550  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 550  
 Leu Glu Val Lys Gly Tyr Glu Asp Gly Gly Ile His Leu Glu Cys Arg  
 1 5 10 15  
 Ser Thr Gly Trp Tyr Pro Gln Pro Gln Ile  
 20 25

<210> 551  
 <211> 80  
 <212> PRT

SUBSTITUTE SHEET (RULE 26)

240

&lt;213&gt; Homo sapiens

&lt;400&gt; 551

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Met Ala Ser Ser Leu Ala Phe Leu Leu Leu Asn Phe His Val Ser Leu
 1             5             10             15

Leu Leu Val Gln Leu Leu Thr Pro Cys Ser Ala Gln Phe Ser Val Leu
          20             25             30

Gly Pro Ser Gly Pro Ile Leu Ala Met Val Gly Glu Asp Ala Asp Leu
      35             40             45

Pro Cys His Leu Phe Pro Thr Met Ser Ala Glu Thr Met Glu Leu Lys
      50             55             60

Trp Val Ser Ser Ser Leu Arg Gln Val Val Asn Val Tyr Ala Asp Gly
 65             70             75             80

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&lt;210&gt; 552

&lt;211&gt; 103

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 552

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Arg His Glu Leu Ser His Asn Arg Lys Asn Gly Glu Leu Leu Ile Asp
 1             5             10             15

Arg Leu Tyr Ser Val Gly Ser Asp Ser Pro Met Gly Ile Pro Arg Asp
      20             25             30

Ile Ile Phe Thr Asp Gly Phe Pro Tyr Trp Asn Pro Lys Val Lys Thr
      35             40             45

Leu Lys Asp Arg His Phe Trp Gln Ser Ile Asp Glu Asn Gly Lys Phe
      50             55             60

Pro Gly Phe Pro Ser Ala Gln Leu Ser Cys Leu Pro Pro Leu Gly Pro
      65             70             75             80

Ala Ala His Ser Leu Leu Ser Ser Val Phe Cys Ala Trp Thr Leu Trp
          85             90             95

Ala His Pro Gly His Gly Gly
      100

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&lt;210&gt; 553

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 553

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Leu Leu Ile Asp Arg Leu Tyr Ser Val Gly Ser Asp Ser Pro Met Gly

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SUBSTITUTE SHEET (RULE 26)

241  
1 5 10 15  
Ile Pro Arg Asp Ile Ile Phe Thr  
20  
<210> 554  
<211> 25  
<212> PRT  
<213> Homo sapiens  
<400> 554  
Asn Pro Lys Val Lys Thr Leu Lys Asp Arg His Phe Trp Gln Ser Ile  
1 5 10 15  
Asp Glu Asn Gly Lys Phe Pro Gly Phe  
20 25  
<210> 555  
<211> 24  
<212> PRT  
<213> Homo sapiens  
<400> 555  
Leu Gly Pro Ala Ala His Ser Leu Leu Ser Ser Val Phe Cys Ala Trp  
1 5 10 15  
Thr Leu Trp Ala His Pro Gly His  
20  
<210> 556  
<211> 135  
<212> PRT  
<213> Homo sapiens  
<400> 556  
Arg Leu Gln His Trp Val Leu Ile Phe Thr Leu Glu Val Lys Gly Tyr  
1 5 10 15  
Glu Asp Gly Gly Ile His Leu Glu Cys Arg Ser Thr Gly Trp Tyr Pro  
20 25 30  
Gln Pro Gln Ile Gln Trp Ser Asn Ala Lys Gly Glu Asn Ile Pro Ala  
35 40 45  
Val Glu Ala Pro Val Val Ala Asp Gly Val Gly Leu Tyr Glu Val Ala  
50 55 60  
Ala Ser Val Ile Met Arg Gly Gly Ser Gly Glu Gly Val Ser Cys Ile  
65 70 75 80  
Ile Arg Asn Ser Leu Leu Gly Leu Glu Lys Thr Ala Ser Ile Ser Ile  
85 90 95  
Ala Asp Pro Ser Ser Gly Ala Pro Ser Pro Gly Ser Gln Pro Trp Gln

SUBSTITUTE SHEET (RULE 26)

242

100                      105                      110

Gly Pro Cys Leu Ser Cys Cys Cys Phe Ser Pro Glu Pro Val Thr Ser  
                  115                      120                      125

Cys Gly Asp Asn Arg Arg Lys  
                  130                      135

<210> 557  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<400> 557  
 Gly Gly Ile His Leu Glu Cys Arg Ser Thr Gly Trp Tyr Pro Gln Pro  
       1                      5                      10                      15

Gln Ile Gln Trp Ser Asn Ala Lys Gly  
                  20                      25

<210> 558  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 558  
 Pro Gln Ile Gln Trp Ser Asn Ala Lys Gly Glu Asn Ile Pro Ala Val  
       1                      5                      10                      15

Glu Ala Pro Val Val Ala Asp Gly Val Gly Leu  
                  20                      25

<210> 559  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 559  
 Asn Ile Pro Ala Val Glu Ala Pro Val Val Ala Asp Gly Val Gly Leu  
       1                      5                      10                      15

Tyr Glu Val Ala Ala Ser Val Ile Met Arg Gly  
                  20                      25

<210> 560  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 560  
 Ser Gly Ala Pro Ser Pro Gly Ser Gln Pro Trp Gln Gly Pro Cys Leu  
       1                      5                      10                      15

**SUBSTITUTE SHEET (RULE 26)**

243

Ser Cys Cys Cys Phe Ser Pro Glu Pro Val Thr  
 20 25

<210> 561  
 <211> 131  
 <212> PRT  
 <213> Homo sapiens

<400> 561  
 Ser Ser Ser Ile Cys Asp His Glu Arg Arg Leu Arg Gly Gly Cys Ile  
 1 5 10 15

Leu His His Gln Lys Phe Pro Pro Arg Pro Gly Lys Asp Ser Gln His  
 20 25 30

Phe His Arg Arg Pro Phe Phe Arg Ser Ala Gln Pro Trp Ile Ala Ala  
 35 40 45

Leu Ala Gly Thr Leu Pro Ile Leu Leu Leu Leu Ala Gly Ala Ser  
 50 55 60

Tyr Phe Leu Trp Arg Gln Gln Lys Glu Ile Thr Ala Leu Ser Ser Glu  
 65 70 75 80

Ile Glu Ser Glu Gln Glu Met Lys Glu Met Gly Tyr Ala Ala Thr Glu  
 85 90 95

Arg Glu Ile Ser Leu Arg Glu Ser Leu Gln Glu Glu Leu Lys Arg Lys  
 100 105 110

Lys Ile Gln Tyr Leu Thr Arg Gly Glu Glu Ser Ser Ser Asp Thr Asn  
 115 120 125

Lys Ser Ala  
 130

<210> 562  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 562  
 Lys Asp Ser Gln His Phe His Arg Arg Pro Phe Phe Arg Ser Ala Gln  
 1 5 10 15

Pro Trp Ile Ala Ala Leu Ala Gly Thr Leu Pro Ile  
 20 25

<210> 563  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 563

**SUBSTITUTE SHEET (RULE 26)**

244

Glu Ile Glu Ser Glu Gln Glu Met Lys Glu Met Gly Tyr Ala Ala Thr  
 1 5 10 15

Glu Arg Glu Ile Ser Leu Arg Glu Ser Leu Gln Glu  
 20 25

&lt;210&gt; 564

&lt;211&gt; 33

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 564

Val Asn Asn Met Ile Ala Phe Tyr Ser Ala Arg Asp Ser Tyr Val Tyr  
 1 5 10 15

Pro His Phe Ser Gly Glu Glu Met Leu Gln Met Arg Leu His Leu Val  
 20 25 30

Lys

&lt;210&gt; 565

&lt;211&gt; 38

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 565

Thr Pro Cys Ser Ala Gln Phe Ser Val Leu Gly Pro Ser Gly Pro Ile  
 1 5 10 15

Leu Ala Met Val Gly Glu Asp Ala Asp Leu Pro Cys His Leu Phe Pro  
 20 25 30

Thr Met Ser Ala Glu Thr  
 35

&lt;210&gt; 566

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 566

Lys Trp Val Ser Ser Ser Leu Arg Gln Val Val Asn Val Tyr Ala Asp  
 1 5 10 15

Gly Lys Glu Val Glu Asp Arg  
 20

&lt;210&gt; 567

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

SUBSTITUTE SHEET (RULE 26)

245

&lt;400&gt; 567

Arg Thr Ser Ile Leu Arg Asp Gly Ile Thr Ala Gly Lys Ala Ala Leu  
 1 5 10 15

Arg Ile His Asn Val Thr Ala Ser Asp  
 20 25

&lt;210&gt; 568

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 568

Cys Tyr Phe Gln Asp Gly Asp Phe Tyr Glu Lys Ala Leu Val Glu Leu  
 1 5 10 15

Lys Val Ala Ala Leu Gly Ser  
 20

&lt;210&gt; 569

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 569

Gly Tyr Glu Asp Gly Gly Ile His Leu Glu Cys Arg Ser Thr Gly Trp  
 1 5 10 15

Tyr Pro Gln Pro Gln Ile Gln  
 20

&lt;210&gt; 570

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 570

Asn Ile Pro Ala Val Glu Ala Pro Val Val Ala Asp Gly Val Gly Leu  
 1 5 10 15

Tyr Glu Val Ala Ala Ser Val  
 20

&lt;210&gt; 571

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 571

Gln Gln Lys Glu Ile Thr Ala Leu Ser Ser Glu Ile Glu Ser Glu Gln  
 1 5 10 15

Glu Met Lys Glu Met

SUBSTITUTE SHEET (RULE 26)

20

&lt;210&gt; 572

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 572

Leu Arg Glu Ser Leu Gln Glu Glu Leu Lys Arg Lys Lys Ile Gln Tyr  
1 5 10 15

Leu Thr Arg Gly Glu Glu Ser Ser  
20

&lt;210&gt; 573

&lt;211&gt; 13

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 573

Gly Glu Glu Met Leu Gln Met Arg Leu His Leu Val Lys  
1 5 10

&lt;210&gt; 574

&lt;211&gt; 40

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 574

Ser Ala Gln Phe Ser Val Leu Gly Pro Ser Gly Pro Ile Leu Ala Met  
1 5 10 15

Val Gly Glu Asp Ala Asp Leu Pro Cys His Leu Phe Pro Thr Met Ser  
20 25 30

Ala Glu Thr Met Glu Leu Lys Trp  
35 40

&lt;210&gt; 575

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 575

Pro Gln Gly Gly Leu Thr Leu Pro Ser Val Trp Gly  
1 5 10

&lt;210&gt; 576

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

SUBSTITUTE SHEET (RULE 26)



247

&lt;400&gt; 576

Gly Gly Pro Cys His Leu Trp Leu Leu Gly Pro Arg Arg Thr Gln Leu  
 1 5 10 15

Pro Gly Arg Arg Ala Ser Leu Pro Phe Arg Ser Gln Gly Glu Leu Thr  
 20 25 30

Gln Ala Phe Leu Leu Gly Leu Trp Lys His Gln Met Pro Ala Leu Thr  
 35 40 45

Gln Glu Gln Gln Val Arg Ala Glu Arg Arg Arg Glu Ala Val Arg Met  
 50 55 60

Glu Ile Pro Gly Leu Phe Phe Ala Ser Leu Ala Asn Trp Gly Leu Leu  
 65 70 75 80

Tyr Arg Thr Ser Gln Asp Phe Ile Ser Pro Tyr Leu Cys Ala Ala Pro  
 85 90 95

Ser Thr Pro His Pro Pro Leu Gly Gly Pro  
 100 105

&lt;210&gt; 577

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 577

Gly Pro Arg Arg Thr Gln Leu Pro Gly Arg Arg Ala Ser Leu Pro Phe  
 1 5 10 15

Arg Ser Gln Gly Glu Leu Thr  
 20

&lt;210&gt; 578

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 578

Gln Met Pro Ala Leu Thr Gln Glu Gln Gln Val Arg Ala Glu Arg Arg  
 1 5 10 15

Arg Glu Ala Val Arg Met Glu Ile  
 20

&lt;210&gt; 579

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 579

Ala Asn Trp Gly Leu Leu Tyr Arg Thr Ser Gln Asp Phe Ile Ser Pro  
 1 5 10 15

SUBSTITUTE SHEET (RULE 26)

Tyr Leu Cys Ala Ala Pro Ser Thr Pro  
                   20                  25

<210> 580  
 <211> 34  
 <212> PRT  
 <213> Homo sapiens

<400> 580  
 Leu Ser Phe Lys Asp Lys Ser Thr Tyr Ile Glu Ser Ser Thr Lys Val  
   1                  5                  10                  15

Tyr Asp Asp Met Ala Phe Arg Tyr Leu Ser Trp Ile Leu Phe Pro Leu  
                   20                  25                  30

Leu Gly

<210> 581  
 <211> 31  
 <212> PRT  
 <213> Homo sapiens

<400> 581  
 Leu Leu Thr Phe Gly Phe Ile Thr Met Thr Pro Gln Leu Phe Ile Asn  
   1                  5                  10                  15

Tyr Lys Leu Lys Ser Val Ala His Leu Pro Trp Arg Met Leu Thr  
                   20                  25                  30

<210> 582  
 <211> 30  
 <212> PRT  
 <213> Homo sapiens

<400> 582  
 Thr Tyr Lys Ala Leu Asn Thr Phe Ile Asp Asp Leu Phe Ala Phe Val  
   1                  5                  10                  15

Ile Lys Met Pro Val Met Tyr Arg Ile Gly Cys Leu Arg Asp  
                   20                  25                  30

<210> 583  
 <211> 30  
 <212> PRT  
 <213> Homo sapiens

<400> 583  
 Asp Val Val Phe Phe Ile Tyr Leu Tyr Gln Arg Trp Ile Tyr Arg Val  
   1                  5                  10                  15

Asp Pro Thr Arg Val Asn Glu Phe Gly Met Ser Gly Glu Asp

**SUBSTITUTE SHEET (RULE 26)**

249

20

25

30

&lt;210&gt; 584

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 584

Val Ala Gly Ile Phe Pro Arg Leu Ser Phe Lys Asp Lys Ser Thr Tyr  
 1 5 10 15

Ile Glu Ser Ser Thr Lys Val Tyr Asp Asp Met Ala Phe Arg Tyr Leu  
 20 25 30

Ser Trp Ile Leu Phe Pro Leu Leu Gly Cys Tyr Ala  
 35 40

&lt;210&gt; 585

&lt;211&gt; 19

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 585

Trp Ala Ala Met Pro Ser Thr Val Phe Cys Thr Trp Ser Thr Arg Ala  
 1 5 10 15

Gly Thr Pro

&lt;210&gt; 586

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 586

Pro Trp Val Ala Gly Ile Phe Pro Arg Leu Ser Phe Lys Asp Lys Ser  
 1 5 10 15

Thr Tyr Ile Glu Ser Ser Thr Lys Val Tyr Asp Asp  
 20 25

&lt;210&gt; 587

&lt;211&gt; 88

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 587

Ala Gly Glu Asp Ser Cys His Pro Val Leu Ser Val Gln Pro Asp Val  
 1 5 10 15

His Asp Leu Gly Trp Gln Glu Ser Ser Pro Ala Tyr Pro Ser Arg Thr  
 20 25 30

SUBSTITUTE SHEET (RULE 26)

250

Ser Pro Arg Ile Ser Ser Pro Arg Pro Lys Cys Met Met Ile Trp His  
 35 40 45

Ser Gly Thr Cys Pro Gly Ser Ser Ser Arg Ser Trp Ala Ala Met Pro  
 50 55 60

Ser Thr Val Phe Cys Thr Trp Ser Thr Arg Ala Gly Thr Pro Gly Cys  
 65 70 75 80

Ser Ala Cys Ser Thr Ala Ser Cys  
 85

&lt;210&gt; 588

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 588

Leu Ser Val Gln Pro Asp Val His Asp Leu Gly Trp Gln Glu Ser Ser  
 1 5 10 15

Pro Ala Tyr Pro Ser Arg Thr Ser Pro Arg Ile Ser Ser Pro  
 20 25 30

&lt;210&gt; 589

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 589

Gly Ser Ser Ser Arg Ser Trp Ala Ala Met Pro Ser Thr Val Phe Cys  
 1 5 10 15

Thr Trp Ser Thr Arg Ala Gly Thr Pro  
 20 25

&lt;210&gt; 590

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 590

Cys Tyr Ala Val Tyr Ser Leu Leu Tyr Leu Glu His Lys Gly Trp Tyr  
 1 5 10 15

Ser Trp Val Leu Ser Met  
 20

&lt;210&gt; 591

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

SUBSTITUTE SHEET (RULE 26)

251

&lt;400&gt; 591

Leu Gly Glu Phe Leu Ser Ser Gln Cys Phe Leu Pro  
 1 5 10

&lt;210&gt; 592

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 592

Arg Ser Arg Arg Asn Arg Val Ala Met Gly Met Trp Ala Ser Leu Asp  
 1 5 10 15

Ala Leu Trp Glu

20

&lt;210&gt; 593

&lt;211&gt; 92

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 593

Pro Arg Val Arg Cys Gln Gln Arg Ala Glu Gly Gly Met Gly Ala Gly  
 1 5 10 15

Ile Gly Val Gly Pro Ser Glu Arg Thr Asp Ile Ala Val Thr Pro Arg  
 20 25 30

Gly Arg Ser Glu Gly Ala Ser Val Gly Val Ala Pro Val His Ala Glu  
 35 40 45

Gly Ala Gly Gly Thr Gly Trp Pro Trp Gly Cys Gly His Arg Trp Thr  
 50 55 60

Leu Cys Gly Arg Cys Arg Pro Arg Ser Val Ser Ser Gly Pro Cys Cys  
 65 70 75 80

Ser Phe Pro Gly Gln Cys Ile Phe Gly Arg Pro Ser  
 85 90

&lt;210&gt; 594

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 594

Gly Gly Met Gly Ala Gly Ile Gly Val Gly Pro Ser Glu Arg Thr Asp  
 1 5 10 15

Ile Ala Val Thr Pro Arg Gly Arg  
 20

&lt;210&gt; 595

SUBSTITUTE SHEET (RULE 26)

252

<211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 595  
 Gly Cys Gly His Arg Trp Thr Leu Cys Gly Arg Cys Arg Pro Arg Ser  
           1                  5                  10                  15  
 Val Ser Ser Gly Pro Cys Cys Ser Phe Pro  
                   20                  25

<210> 596  
 <211> 24  
 <212> PRT  
 <213> Homo sapiens

<400> 596  
 Lys Lys His Gly Phe Asn Gln Gln Thr Leu Gly Phe Phe Thr Trp Lys  
           1                  5                  10                  15  
 Tyr Asn Lys Asn Lys Asn Leu Val  
                   20

<210> 597  
 <211> 21  
 <212> PRT  
 <213> Homo sapiens

<400> 597  
 Pro Lys Leu Leu Pro Cys Ser Pro Ala Glu Gly His Thr Ser Leu Gly  
           1                  5                  10                  15  
 Pro Leu Leu Pro Phe  
                   20

<210> 598  
 <211> 70  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (6)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 598  
 Ala Ser Leu Glu Leu Xaa Pro Ser Lys Ser Gln Leu Ser Thr Glu Trp  
           1                  5                  10                  15  
 Gly Phe Thr Trp Ile Val Gly Leu Gly Met Ser Pro Ser Thr Ala Leu  
                   20                  25                  30  
 Trp Thr Glu Cys Thr Cys Thr Pro Phe Leu Val Leu Leu Ser His Ala  
           35                  40                  45

SUBSTITUTE SHEET (RULE 26)

253

Ser Gly His Phe Phe Trp Leu Ser Pro Leu Ala Ser Leu Val Ile Pro  
 50 55 60

Pro Val Thr Asp Arg Lys  
 65 70

<210> 599  
 <211> 32  
 <212> PRT  
 <213> Homo sapiens

<400> 599  
 Trp Gly Phe Thr Trp Ile Val Gly Leu Gly Met Ser Pro Ser Thr Ala  
 1 5 10 15

Leu Trp Thr Glu Cys Thr Cys Thr Pro Phe Leu Val Leu Leu Ser His  
 20 25 30

<210> 600  
 <211> 106  
 <212> PRT  
 <213> Homo sapiens

<400> 600  
 Val Ala Val Gly Val Cys Arg Glu Asp Val Met Gly Ile Thr Asp Arg  
 1 5 10 15

Ser Lys Met Ser Pro Asp Val Gly Ile Trp Ala Ile Tyr Trp Ser Ala  
 20 25 30

Ala Gly Tyr Trp Pro Leu Ile Gly Phe Pro Gly Thr Pro Thr Gln Gln  
 35 40 45

Glu Pro Ala Leu His Arg Val Gly Val Tyr Leu Asp Arg Gly Thr Gly  
 50 55 60

Asn Val Ser Phe Tyr Ser Ala Val Asp Gly Val His Leu His Thr Phe  
 65 70 75 80

Ser Cys Ser Ser Val Ser Arg Leu Arg Pro Phe Phe Leu Val Glu Ser  
 85 90 95

Ile Ser Ile Phe Ser His Ser Thr Ser Asp  
 100 105

<210> 601  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

SUBSTITUTE SHEET (RULE 26)

254

&lt;400&gt; 601

Ile Thr Asp Arg Ser Lys Met Ser Pro Asp Val Gly Ile Trp Ala Ile  
1 5 10 15

Tyr Trp Ser Ala Ala Gly Tyr Trp Pro Leu Ile  
20 25

&lt;210&gt; 602

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 602

Arg Gly Thr Gly Asn Val Ser Phe Tyr Ser Ala Val Asp Gly Val His  
1 5 10 15

Leu His Thr Phe Ser Cys Ser Ser Val Ser Arg Leu Arg Pro  
20 25 30

&lt;210&gt; 603

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 603

Gly Thr Arg Gly Leu Gln Asn His Arg Thr Glu  
1 5 10

&lt;210&gt; 604

&lt;211&gt; 6

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 604

Glu Leu Ser Gly Leu Gly  
1 5

&lt;210&gt; 605

&lt;211&gt; 6

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 605

Met Asp Asp Ile Lys Ile  
1 5

&lt;210&gt; 606

&lt;211&gt; 57

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 606

SUBSTITUTE SHEET (RULE 26)



255

Asn Phe Cys Val Ser Lys Asn Thr Phe Asn Arg Val Lys Arg Pro Ile  
 1 5 10 15

Lys Trp Val Lys Ile Phe Ala Asn Asp Ile Ser Cys Lys Arg Leu Ile  
 20 25 30

Ser Arg Ile His Lys Glu Ile Leu Pro Phe Asn Asn Lys Lys Gln Pro  
 35 40 45

Asp Phe Lys Val Lys Lys Ser Arg Lys  
 50 55

&lt;210&gt; 607

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 607

Phe Asn Arg Val Lys Arg Pro Ile Lys Trp Val Lys Ile Phe Ala Asn  
 1 5 10 15

Asp Ile Ser Cys Lys Arg Leu Ile Ser Arg Ile His Lys Glu  
 20 25 30

&lt;210&gt; 608

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 608

Glu Thr Gln Met Ala Asn Lys Tyr Met Lys Arg Cys Ser Thr Leu  
 1 5 10 15

&lt;210&gt; 609

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 609

Val Ile Arg Glu Leu Gln Val Lys Ala Thr Arg Arg Cys His Tyr Thr  
 1 5 10 15

Pro Ile Lys Trp Ser Lys Ser Lys Thr Leu Ile Ser Ser Asn Ala Asp  
 20 25 30

Glu Tyr Val Glu Pro Thr Arg Thr Leu Ile His Cys Trp Trp Lys Cys  
 35 40 45

Lys Ile Val Gln Pro Leu Cys Lys Thr Ala Trp  
 50 55

&lt;210&gt; 610

&lt;211&gt; 22

SUBSTITUTE SHEET (RULE 26)

256

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 610

Ala Thr Arg Arg Cys His Tyr Thr Pro Ile Lys Trp Ser Lys Ser Lys  
 1 5 10 15

Thr Leu Ile Ser Ser Asn  
 20

&lt;210&gt; 611

&lt;211&gt; 64

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 611

Glu Leu Ser Gly Leu Val Ile Ile Thr Ala Trp Ile Ile Leu Cys His  
 1 5 10 15

Ser Ser Ser Lys Asn Pro Val Gly Gly Arg Ile Gln Leu Ala Ile Ala  
 20 25 30

Ile Val Ile Thr Leu Phe Pro Phe Ile Ser Trp Val Tyr Ile Tyr Ile  
 35 40 45

Asn Lys Glu Met Arg Ser Ser Trp Pro Thr His Cys Lys Thr Val Ile  
 50 55 60

&lt;210&gt; 612

&lt;211&gt; 57

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 612

Gln Cys Pro Gln Gly Thr Glu Thr Glu Ala Gly Val Ser Val Pro Pro  
 1 5 10 15

Arg Lys Glu Gly Gly Gly Pro Tyr Val Ala Gly Leu Thr Ala Pro His  
 20 25 30

Val Ala Gly Leu Thr Ala Pro Arg Arg Val Leu Arg Ala Met Ala Pro  
 35 40 45

Ala Leu Trp Arg Ala Cys Asn Gly Leu  
 50 55

&lt;210&gt; 613

&lt;211&gt; 32

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

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257

&lt;400&gt; 613

His Ser Ser Ser Lys Asn Pro Val Gly Gly Arg Ile Gln Leu Ala Ile  
1 5 10 15

Ala Ile Val Ile Thr Leu Phe Pro Phe Ile Ser Trp Val Tyr Ile Tyr  
20 25 30

&lt;210&gt; 614

&lt;211&gt; 32

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 614

Arg Lys Glu Gly Gly Gly Pro Tyr Val Ala Gly Leu Thr Ala Pro His  
1 5 10 15

Val Ala Gly Leu Thr Ala Pro Arg Arg Val Leu Arg Ala Met Ala Pro  
20 25 30

&lt;210&gt; 615

&lt;211&gt; 32

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (9)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 615

Pro Gly Arg Pro Thr Arg Pro Ala Xaa Ala Gly Leu Ser Ser Gly Gly  
1 5 10 15

Ala Ala Gln Glu Ala Pro Gln Ala Asp Pro Arg Pro Trp Leu Ala Arg  
20 25 30

&lt;210&gt; 616

&lt;211&gt; 51

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (3)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

SUBSTITUTE SHEET (RULE 26)

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (29)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 616

His Tyr Xaa Ser Thr Pro Gly Arg Val Pro Val Arg Gln Phe Ala Ala  
 1 5 10 15

Ala Ser Thr Ser Gly Gly Pro Trp Val Pro Gly Gly Xaa Leu Glu Ala  
 20 25 30

Pro Phe Gln Val Ala Pro Ser Leu Ser His Ser Thr Pro Val Phe Pro  
 35 40 45

Gly Leu Ile  
 50

&lt;210&gt; 617

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 617

Ala Arg Gly Lys Tyr Glu Ser Ala Gln Pro Gly Gly Thr Gln Pro Glu  
 1 5 10 15

Pro Gly Leu Gly Ala Arg  
 20

&lt;210&gt; 618

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 618

Ser Cys Gly Ser Ser Arg Arg Ser Ala Lys Arg Ser Leu Thr Leu Lys  
 1 5 10 15

Leu Ile Asp Phe Ser His Arg Ile  
 20

&lt;210&gt; 619

&lt;211&gt; 52

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 619

His Tyr Phe Leu Arg Thr Val Ser Gly Leu Ser Val Val Pro Val Ser  
 1 5 10 15

Leu Arg Cys Cys Met Cys Pro Pro Pro Cys Thr Gly Pro Ala Pro Ala  
 20 25 30

SUBSTITUTE SHEET (RULE 26)

Thr Ala His Ser Pro Phe Asp Pro Pro Ala Leu Pro Ile Gln Phe Glu  
                   35                                  40                                  45

Tyr Gln Gln Ala  
                   50

<210> 620  
 <211> 45  
 <212> PRT  
 <213> Homo sapiens

<400> 620  
 Gln Leu Glu Ala Glu Ile Glu Asn Leu Ser Trp Lys Val Glu Arg Ala  
           1                                  5                                  10                                  15

Asp Ser Tyr Asp Arg Gly Asp Leu Glu Asn Gln Met His Ile Ala Glu  
                                   20                                  25                                  30

Gln Arg Arg Arg Thr Leu Leu Lys Asp Phe His Asp Thr  
                   35                                  40                                  45

<210> 621  
 <211> 24  
 <212> PRT  
 <213> Homo sapiens

<400> 621  
 Val Pro Val Ser Leu Arg Cys Cys Met Cys Pro Pro Pro Cys Thr Gly  
           1                                  5                                  10                                  15

Pro Ala Pro Ala Thr Ala His Ser  
                   20

<210> 622  
 <211> 25  
 <212> PRT  
 <213> Homo sapiens

<400> 622  
 Ser Trp Lys Val Glu Arg Ala Asp Ser Tyr Asp Arg Gly Asp Leu Glu  
           1                                  5                                  10                                  15

Asn Gln Met His Ile Ala Glu Gln Arg  
                   20                                  25

<210> 623  
 <211> 227  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE

**SUBSTITUTE SHEET (RULE 26)**

260

&lt;222&gt; (53)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 623

His Glu Ala Trp Leu Arg Ser Ala Gly Thr Arg Glu Pro Pro Arg Glu  
 1 5 10 15

Gln Arg Thr Arg Arg Arg Gln Thr Ala Gln Leu Ala Leu Gln Val Pro  
 20 25 30

Ala Pro Ser Arg Thr Pro Pro Met Ala Thr Asp Val Phe Asn Ser Lys  
 35 40 45

Asn Leu Ala Val Xaa Ala Gln Lys Lys Ile Leu Gly Lys Met Val Ser  
 50 55 60

Lys Ser Ile Ala Thr Thr Leu Ile Asp Asp Thr Ser Ser Glu Val Leu  
 65 70 75 80

Asp Glu Leu Tyr Arg Val Thr Arg Glu Tyr Thr Gln Asn Lys Lys Glu  
 85 90 95

Ala Glu Lys Ile Ile Lys Asn Leu Ile Lys Thr Val Ile Lys Leu Ala  
 100 105 110

Ile Leu Tyr Arg Asn Asn Gln Phe Asn Gln Asp Glu Leu Ala Leu Met  
 115 120 125

Glu Lys Phe Lys Lys Lys Val His Gln Leu Ala Met Thr Val Val Ser  
 130 135 140

Phe His Gln Val Asp Tyr Thr Phe Asp Arg Asn Val Leu Ser Arg Leu  
 145 150 155 160

Leu Asn Glu Cys Arg Glu Met Leu His Gln Ile Ile Gln Arg His Leu  
 165 170 175

Thr Ala Lys Ser His Gly Arg Val Asn Asn Val Phe Asp His Phe Ser  
 180 185 190

Asp Cys Glu Phe Leu Ala Ala Leu Tyr Asn Pro Phe Gly Asn Phe Lys  
 195 200 205

Pro His Leu Gln Lys Leu Cys Asp Gly Ile Asn Lys Met Leu Asp Glu  
 210 215 220

Glu Asn Ile  
 225

&lt;210&gt; 624

&lt;211&gt; 52

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 624

His Glu Ala Trp Leu Arg Ser Ala Gly Thr Arg Glu Pro Pro Arg Glu

SUBSTITUTE SHEET (RULE 26)

<210> 627  
<211> 52

**SUBSTITUTE SHEET (RULE 26)**

262

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 627

Asp Arg Asn Val Leu Ser Arg Leu Leu Asn Glu Cys Arg Glu Met Leu  
1 5 10 15

His Gln Ile Ile Gln Arg His Leu Thr Ala Lys Ser His Gly Arg Val  
20 25 30

Asn Asn Val Phe Asp His Phe Ser Asp Cys Glu Phe Leu Ala Ala Leu  
35 40 45

Tyr Asn Pro Phe  
50

&lt;210&gt; 628

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 628

Gly Asn Phe Lys Pro His Leu Gln Lys Leu Cys Asp Gly Ile Asn Lys  
1 5 10 15

Met Leu Asp Glu Glu Asn Ile  
20

SUBSTITUTE SHEET (RULE 26)



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/27059

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C07H 21/00; C12N 1/15, 1/21, 5/10, 15/11, 15/63

US CL : 435/91.41, 320.1, 325, 252.3, 254.11; 536/23.1, 23.5, 24.31

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/91.41, 320.1, 325, 252.3, 254.11; 536/23.1, 23.5, 24.31

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

GENBANK, EMBL, SWISS-PROT, SPTREMBL, PIR,  
searched: SEQ ID NO: 11-20 & 125-134

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), No. AA133381, HILLIER et al. 'WashU-Merck EST Project', complete record, 27 November 1996.	1, 7-10
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), No. T12400, LIEW et al. 'A catalogue of genes in the cardiovascular system as identified by expressed sequence tags', complete record, 27 November 1996.	1, 7-10
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), No. AA496982, HILLIER et al. 'WashU-Merck EST Project 1997', complete record, 12 August 1997.	1, 7-10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

02 MARCH 1999

Date of mailing of the international search report

23 MAR 1999

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
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Washington, D.C. 20231

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Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)\*

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/27059

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), No. U14626, D'ALESSIO et al. 'Cloning vector pSVSport1', complete record, 24 May 1995.	1, 7-10
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), No. AJ000730, SPERANDEO et al. 'The full cDNA for the human cationic amino acid transporter 3 (HCAT3)', complete record, 02 December 1997.	1
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), No. R31044, HILLIER et al. 'The WashU-Merck EST Project', complete record, 28 April 1995.	1, 7-10
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), No. AA446873, HILLIER et al. 'WashU-Merck EST Project 1997', complete record, 03 June 1997.	1, 7-10
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), No. AA135715, HILLIER et al. 'WashU-Merck EST Project', complete record, 14 May 1997.	1, 7-10
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), No. AA194015, HILLIER et al. 'WashU-Merck EST Project', complete record, 19 May 1997.	1, 7-10
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), No. R72850, HILLIER et al. 'The WashU-Merck EST Project', complete record, 02 June 1995.	1, 7-10
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), No. T60940, HILLIER et al. 'WashU-Merck EST Project', complete record, 13 February 1995.	1, 7-10
X	Database GenBank, US National Library of Medicine, (Bethesda, MD, USA), No. H86863, HILLIER et al. 'The WashU-Merck EST Project', complete record, 21 November 1995.	1, 7-10

Form PCT/ISA/210 (continuation of second sheet)(July 1992)★

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/27059

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-10, 21

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/27059

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Groups I-XXVII, claim(s) 1-10 and 21, drawn to a polynucleotide, vector comprising same, first claimed method of use, i.e. using polynucleotide to make a cell, and the cell made by the process. Claims 1-10 and 21 recite 114 independent polynucleotides (SEQ ID NO: 11-124 or encoding SEQ ID NO: 125-238). Group I consists of the first ten polynucleotides (SEQ ID NOs 11-20 or encoding SEQ ID NOs 125-134). Each of groups II-XXVII consists of up to four of the remaining 104 polynucleotides, in order.

Groups XXVIII-CXLI, claim(s) 11, 12, 14-16 and 17 (first part), drawn to a polypeptide, a method of making the polypeptide and first claimed method of use, i.e. in treatment. These claims recite 114 independent polypeptides, each of groups XXVIII-CXLI consists of a single polypeptide as set forth in SEQ ID NOs 125-238, respectively.

Groups CXLI-CCLV, claim(s) 13 and 19, drawn to an antibody to a polypeptide and the first claimed method of using same. These claims recite 114 independent antibodies to 114 independent polypeptides, each of groups CXLI-CCLV consists an antibody against a single polypeptide as set forth in SEQ ID NOs 125-238, respectively.

Groups CCLVI-CCLXXXII, claim(s) 17(second part), drawn to an additional method of using a polynucleotide. Group CCLVI consists of methods reciting the first ten polynucleotides (SEQ ID NOs 11-20 or encoding SEQ ID NOs 125-134). Each of groups CCLVII-CCLXXXII pertains to up to four of the remaining 104 polynucleotides, in order.

Groups CCLXXXIII-CCCIX, claim(s) 18, drawn to a second additional method of using a polynucleotide. Group CCLXXXIII consists of methods reciting the first ten polynucleotides (SEQ ID NOs 11-20 or encoding SEQ ID NOs 125-134). Each of groups CCLXXXIV-CCCIX pertains to up to four of the remaining 104 polynucleotides, in order.

Groups CCCX-CDXXXIII, claim(s) 20, drawn to an additional method of using the polypeptide. These claims recite 114 independent methods of using 114 independent polypeptides, each of groups CCCX-CDXXXIII consists an antibody against a single polypeptide as set forth in SEQ ID NOs 125-238, respectively.

Groups CDXXXIV-CDL, claim 22, drawn to a third additional method of using a polynucleotide. Group CDXXXIV consists of methods reciting the first ten polynucleotides (SEQ ID NOs 11-20 or encoding SEQ ID NOs 125-134). Each of groups CDXXXV-CDL pertains to up to four of the remaining 53 polynucleotides, in order.

Claim 23 is unsearchable and cannot be grouped as it is drawn to unknown and unspecified compounds.

The inventions listed as Groups I-CDL do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Each of the corresponding polynucleotides, polypeptides and antibodies are independent products, with different uses and being structurally, biochemically and biologically different products. Additional or alternate methods of use are claimed for individual polynucleotides and polypeptides. 37 CFR 1.475(b) does not provide for unity of invention of more than 1 product or more than one method of using a product as a combination of invention having unity of invention. However, with respect to groups drawn to independent polynucleotides or alternate methods of using same recited in the alternative, in accordance with 1192 O.G. 68 (19 November 1966) applicant is entitled to an initial search of inventions pertaining to the first ten independent polynucleotides recited, and may elect to pay an additional fee for each search of up to four additional independent polynucleotides. For additional method of using each of the independent polynucleotides, applicant may further elect to pay an additional fee for an additional search involving the first ten polynucleotides and each additional search involving up to four additional polynucleotides. With respect to groups pertaining to independent polypeptides or antibodies to the independent polypeptides, each product or method of use is an additional invention. An additional fee must be paid for search of each additional invention relating to polypeptides or antibodies against same. With respect to the relationship between the claimed polynucleotides and the claimed polypeptides, there is no one-to-one correspondence, i.e. no corresponding scope, between claims drawn to polynucleotides and their use and those drawn to polypeptides, antibodies and their use. Consequently, there is no special technical feature linking the polynucleotides and the polypeptides or antibodies claimed.

